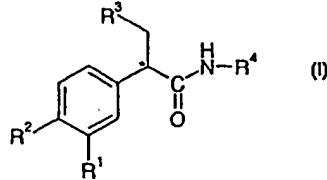


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(54) Title: GLUCOKINASE ACTIVATORS			
			
(57) Abstract			
<p>The present invention relates to compounds of formula (I) wherein R¹, R², R³ and R⁴ are as defined in claim 1 and pharmaceutically acceptable salts thereof. The compounds are glucokinase activators which increase insulin secretion in the treatment of type II diabetes.</p>			

Glucokinase activators

Glucokinase (GK) is one of four hexokinases that are found in mammals [Colowick, S.P., in *The Enzymes*, Vol. 9 (P. Boyer, ed.) Academic Press, New York, NY, pages 1-48, 1973]. The hexokinases catalyze the first step in the metabolism of glucose, i.e., the conversion of glucose to glucose-6-phosphate. Glucokinase has a limited cellular distribution, being found principally in pancreatic β -cells and liver parenchymal cells. In addition, GK is a rate-controlling enzyme for glucose metabolism in these two cell types that are known to play critical roles in whole-body glucose homeostasis [Chipkin, S.R., Kelly, K.L., and Ruderman, N.B. in *Joslin's Diabetes* (C.R. Khan and G.C. Wier, eds.), Lea and Febiger, Philadelphia, PA, pages 97-115, 1994]. The concentration of glucose at which GK demonstrates half-maximal activity is approximately 8 mM. The other three hexokinases are saturated with glucose at much lower concentrations (<1 mM). Therefore, the flux of glucose through the GK pathway rises as the concentration of glucose in the blood increases from fasting (5 mM) to postprandial (\approx 10-15 mM) levels following a carbohydrate-containing meal [Printz, R.G., Magnuson, M.A., and Granner, D.K. in *Ann. Rev. Nutrition* Vol. 13 (R.E. Olson, D.M. Bier, and D.B. McCormick, eds.), Annual Review, Inc., Palo Alto, CA, pages 463-496, 1993]. These findings contributed over a decade ago to the hypothesis that GK functions as a glucose sensor in β -cells and hepatocytes (Meglasson, M.D. and Matschinsky, F.M. *Amer. J. Physiol.* **246**, E1-E13, 1984). In recent years, studies in transgenic animals have confirmed that GK does indeed play a critical role in whole-body glucose homeostasis. Animals that do not express GK die within days of birth with severe diabetes while animals overexpressing GK have improved glucose tolerance (Grupe, A., Hultgren, B., Ryan, A. et al., *Cell* **83**, 69-78, 1995; Ferrie, T., Riu, E., Bosch, F. et al., *FASEB J.*, **10**, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in β -cells to increased insulin secretion and in hepatocytes to increased glycogen deposition and perhaps decreased glucose production.

R⁴ is -C(O)NHR⁴⁰; or an unsubstituted or mono-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amine group shown, which five- or six-membered heteroaromatic ring contains from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono-substituted heteroaromatic ring being monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano, -(CH₂)_n-OR⁶, -(CH₂)_n-C(O)OR⁷, -(CH₂)_n-C(O)NHR⁶, -C(O)-C(O)OR⁸, -(CH₂)_n-NHR⁶;

5 R⁴⁰ is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl, -(CH₂)_n-C(O)OR⁵ or -C(O)-(CH₂)_n-C(O)OR⁶;

R⁵ is hydrogen, lower alkyl or perfluoro-lower alkyl;

R⁶, R⁷ and R⁸ are independently hydrogen or lower alkyl; and

n is 0, 1, 2, 3 or 4;

10 15 or a pharmaceutically acceptable salt thereof.

In the compound of formula I, the * indicates the asymmetric carbon atom in this compound. The compound of formula I may be present either as a racemate or in the "R" configuration at the asymmetric carbon shown. The "R" enantiomers are preferred.

20

The compounds of formula I have been found to activate glucokinase *in vitro*. Glucokinase activators are useful for increasing insulin secretion in the treatment of type II diabetes.

25

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier and/or adjuvant. Furthermore the present invention relates to the use of such compounds for the

As used herein, "lower alkyl sulfinyl" means a lower alkyl group as defined above where a sulfinyl group is bound to the rest of the molecule.

As used herein, "hydroxyamino" designates an amino group where one of the hydrogens is replaced by a hydroxy.

5 As used herein, "cycloalkyl" means a saturated hydrocarbon ring having from 3 to 10 carbon atoms, preferably from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. A preferred cycloalkyl is cyclopentyl.

10 As used herein, the term "lower alkenyl" denotes an alkylene group having from 2 to 6 carbon atoms with a double bond located between any two adjacent carbons of the group. Preferred lower alkenyl groups are allyl and crotyl.

As used herein, the term "lower alkoxy" includes both straight chain and branched chain alkoxy groups having from 1 to 7 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, preferably methoxy and ethoxy.

15 As used herein, the term "aryl" signifies aryl mononuclear aromatic hydrocarbon groups such as phenyl, tolyl, etc. which can be unsubstituted or substituted in one or more positions with halogen, nitro, lower alkyl, or lower alkoxy substituents and polynuclear aryl groups, such as naphthyl, anthryl, and phenanthryl, which can be unsubstituted or substituted with one or more of the aforementioned groups. Preferred aryl groups are the substituted and unsubstituted mononuclear aryl groups, particularly phenyl. The term
20 "arylalkyl" denotes an alkyl group, preferably lower alkyl, in which one of the hydrogen atoms is replaced by an aryl group. Examples of arylalkyl groups are benzyl, 2-phenylethyl, 3-phenylpropyl, 4-chlorobenzyl, 4-methoxybenzyl and the like.

25 As used herein, the term "lower alkanoic acid" denotes lower alkanoic acids containing from 2 to 7 carbon atoms such as propionic acid, acetic acid and the like. The term "lower alkanoyl" denotes monovalent alkanoyl groups having from 2 to 7 carbon atoms such as propionoyl, acetyl and the like. The term "aroic acids" denotes aryl alkanoic acids where aryl is as defined above and alkanoic contains from 1 to 6 carbon atoms. The term "aroyl" denotes aroic acids wherein aryl is as defined hereinbefore, with

dicarboxycyclic acid. Among the activated acids which can be utilized to form such groups are acid anhydrides, acid halides, preferably acid chlorides or acid bromides derived from aryl or lower alkanoic acids. Example of anhydrides are anhydrides derived from monocarboxylic acid such as acetic anhydride, benzoic acid anhydride, and lower 5 alkane dicarboxycyclic acid anhydrides, e.g. succinic anhydride as well as chloro formates e.g. trichloro, ethylchloro formate being preferred. A suitable ether protecting group for alcohols are, for example, the tetrahydropyranyl ethers such as 4-methoxy-5,6-dihydroxy-2H-pyranyl ethers. Others are aroylmethylethers such as benzyl, benzhydryl or trityl ethers or α -lower alkoxy lower alkyl ethers, for example, methoxymethyl or allylic ethers 10 or alkyl silylethers such as trimethylsilylether.

The term "amino protecting group" designates any conventional amino protecting group which can be cleaved to yield the free amino group. The preferred protecting groups are the conventional amino protecting groups utilized in peptide synthesis. Especially preferred are those amino protecting groups which are cleavable under mildly 15 acidic conditions from about pH 2.0 to 3. Particularly preferred amino protecting groups are t-butoxycarbonyl (BOC), carbobenzyloxy (CBZ) and 9-fluorenylmethoxycarbonyl (FMOC).

The term "pharmaceutically acceptable salts" as used herein include any salt with both inorganic or organic pharmaceutically acceptable acids such as hydrochloric acid, 20 hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, *para*-toluene sulfonic acid and the like. The term "pharmaceutically acceptable salts" also includes any pharmaceutically acceptable base salt such as amine salts, trialkyl amine salts and the like. Such salts can be formed quite readily by those skilled in the art using standard 25 techniques.

R³ is cycloalkyl having from 3 to 7 carbon atoms or lower alkyl having from 2 to 4 carbon atoms;

R⁴ is -C(O)NHR⁴⁰;

R⁴⁰ is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl,
5 -(CH₂)_n-C(O)OR⁵ or -C(O)-(CH₂)_n-C(O)OR⁶;

R⁵ and R⁶ are hydrogen or lower alkyl; and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

10 Preferable heteroaromatic residues in R⁴ are unsubstituted or mono-substituted five- or six-membered heteroaromatic rings selected from the group consisting of thiazolyl, pyridinyl, imidazolyl, isoxazolyl, oxazolyl, pyridazinyl, pyrimidinyl or thiadiazolyl. Especially preferred are unsubstituted thiazolyl, unsubstituted pyridinyl or pyridinyl substituted by halogen, lower alkyl, hydroxy lower alkyl or -C(O)OR⁵, wherein
15 R⁵ is lower alkyl.

Preferable residues R⁴⁰ in accordance with the present invention are lower alkyl or lower alkenyl.

Preferable residues R¹ in accordance with the present invention are hydrogen, halo, nitro and cyano, more preferable are hydrogen or halo.

20 Preferable residues R² in accordance with the present invention are hydrogen, lower alkyl sulfonyl, perfluoro-lower alkyl, perfluoro-lower alkyl sulfonyl, halo or -OR⁵ wherein R⁵ is perfluoro-lower alkyl; more preferable are halo or lower alkyl sulfonyl.

Preferable residues R³ in accordance with the present invention are cyclopentyl, cyclohexyl or cycloheptyl, more preferable is cyclopentyl.

25

In the compounds described below, unless otherwise indicated, R⁴ is a group -C(O)NHR⁴⁰, wherein R⁴⁰ is as defined above.

In further amides of the above compound, one of R¹ and R² is hydrogen, lower alkyl thio or perfluoro-lower alkyl thio and the other is lower alkyl thio or perfluoro-lower alkyl thio. Examples of such amides are:

1-[3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)-propionyl]-3-methyl urea;

5 1-[3-cyclopentyl-2-(4-methylsulfanyl-phenyl)-propionyl]-3-methyl urea.

In yet further amides of the above compound, one of R¹ and R² is hydrogen or perfluoro-lower alkyl sulfonyl and the other is perfluoro-lower alkyl sulfonyl. Examples of such amides are:

1-[3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionyl]-3-methyl urea;

10 1-[3-cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionyl]-3-methyl urea.

In certain amides of the above compound, at least one of R¹ and R² is lower alkyl sulfonyl. Preferably one of R¹ and R² is hydrogen or lower alkyl sulfonyl and the other is lower alkyl sulfonyl, and more preferably R² is lower alkyl sulfonyl. Examples of such amides are:

15 1-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionyl]-3-methyl urea;

1-[2-[4-(butane-1-sulfonyl)-phenyl]-3-cyclopentyl-proprionyl]-3-methyl-urea;

1-[3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-proprionyl]-3-methyl-urea;

1-[2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-proprionyl]-3-methyl-urea.

In other amides of the above compound, at least one of R¹ and R² is lower alkyl sulfonyl, one of R¹ and R² is cyano or halo and the other, preferably R², is lower alkyl sulfonyl. Examples of such amides are:

1-[2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-proprionyl]-3-methyl-urea;

1-[3-cyclopentyl-2-(3-fluoro-4-methanesulfonyl-phenyl)-proprionyl]-3-methyl-urea;

1-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-proprionyl]-3-methyl-urea;

25 1-[2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-proprionyl]-3-methyl-urea;

1-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-proprionyl]-3-ethyl-urea;

1-[2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-proprionyl]-3-methyl-urea.

In other amides of the above compound, at least one of R¹ and R² is lower alkyl sulfonyl, one of R¹ and R² is perfluoro-lower alkyl and the other, preferably R², is lower

In certain compounds of this invention, R⁴⁰ is -(CH₂)_n-C(O)OR⁵ or -C(O)-(CH₂)_n-C(O)OR⁶. In some such compounds, R³ of the amide is cyclopentyl. Preferably R¹ and R² are independently halo. Examples of the above amides are:

3-[3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido]-propionic acid ethyl ester;
5 {3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester;
{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid methyl ester;
3-[3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido]-propionic acid methyl ester;
10 {3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester;
3-[3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido]-3-oxo-propionic acid ethyl ester.

In certain compounds of this invention, R⁴⁰ is hydroxy lower alkyl, or halo lower alkyl. In some such compounds, R³ of the amide is cyclopentyl. Preferably R¹ and R² are independently halo, and in addition the amide is in the "R" configuration at the asymmetric carbon shown. Examples of the above amides are:

1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea;
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea;
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea;
20 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea;
1-(2-chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea;
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea.

In the compounds described below, unless otherwise indicated, R⁴ is an unsubstituted or mono-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amine group shown, which five- or six-membered heteroaromatic ring contains from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono-substituted heteroaromatic ring being monosubstituted at a

-15-

- b) one of R¹ and R² is lower alkyl sulfonyl, and the other of said R¹ and R² is lower alkyl sulfonyl or hydrogen; and
- c) one of R¹ and R² is hydrogen and the other of said R¹ and R² is lower alkyl or perfluoro-lower alkyl.

5 In accordance with another embodiment of the invention where R³ is cyclopentyl and R⁴ is a mono-substituted thiazole (Compounds I-D2), are those compounds where the mono-substitution is lower alkyl and one of R¹ and R² are hydrogen or halogen and the other of R¹ and R² is halogen (Compounds I-D2(b)).

Among another embodiment of the compounds I-D are those compounds where
10 the mono-substituted thiazole is substituted with -(CH₂)_n-C(O)OR⁷, wherein n is 0 or 1 and R⁷ is hydrogen, or lower alkyl (Compounds of I-D2(c)). Among the embodiments of compounds of formula I-D2(c) are those compounds where:

- a) one of R¹ and R² is hydrogen and the other of said R¹ and R² is halo;
- b) R¹ and R² are each independently halo;
- c) one of R¹ or R² is nitro, amino or hydrogen and the other of said R¹ and R² is nitro or amino; and
- d) one of R¹ and R² is lower alkyl sulfonyl, perfluoro-lower alkyl, halogen or hydrogen and the other of said R¹ and R² is lower alkyl sulfonyl.

In accordance with another embodiment of this invention, where R³ and
20 cyclopentyl and R⁴ is a mono-substituted thiazole (Compounds I-D2) are those compounds where the mono-substituted thiazole is substituted with -C(O)-C(O)OR⁸, wherein R⁸ is as above (Compounds I-D2(d)). Among the embodiments of compound I-D2(d) are those compounds where:

- a) one of R¹ and R² are hydrogen and the other of said R¹ and R² is nitro or amino;
- b) one of R¹ and R² is halo or perfluoro-lower alkyl and the other of said R¹ and R² is perfluoro-lower alkyl, halogen or hydrogen; and
- c) one of R¹ and R² is hydrogen or halogen and the other of said R¹ and R² is lower alkylsulfonyl.

Other embodiments of the compounds of formula I-D4(b) are those compounds where the pyridine ring is mono-substituted with $-(CH_2)_n-OR^6$ wherein n and R⁶ are as above (Compounds I-D4(b)). Among the embodiments of the compound I-D4(b) are those compounds where:

- 5 a) one of R¹ and R² are halo and the other of said R¹ and R² is hydrogen or halo; and
- b) one of R¹ and R² is lower alkyl sulfonyl or hydrogen and the other of said R¹ and R² is lower alkyl sulfonyl.

Another embodiment of compounds where R³ is cyclopentyl and R⁴ is a mono-substituted pyridine ring are those compounds where the pyridine ring is mono-substituted with a halo or perfluoro-lower alkyl substituent, the compound of formula I-D4(c). Among the embodiments of the compound of formula I-D4(c) are those compounds where:

- 10 a) one of R¹ and R² is halo or hydrogen and the other is halo; and
- b) one of R¹ and R² is halo, nitro or hydrogen and the other is perfluoro-lower alkyl sulfonyl or lower alkyl sulfonyl.

In accordance with another embodiment of this invention are compounds of where R³ is cyclopentyl and R⁴ is a mono-substituted pyridine are those compounds where the pyridine is mono-substituted with a nitro substituent, (Compound I-D4(d)). The embodiments of the compound I-D4(d) include compounds where one of R¹ and R² is halo and other of said R¹ or R² is hydrogen, halo, or lower alkyl sulfonyl.

In accordance with another embodiment of this invention are compounds of formula I where R³ is cyclopentyl and R⁴ is mono-substituted pyridine and the mono-substitution is a lower alkyl group (Compounds I-D4(e)). Among the embodiments of compounds I-D4(e) are those compounds where one of R¹ and R² is halo or hydrogen and the other of R¹ and R² is halo, perfluoro-lower alkyl, perfluoro-lower alkyl sulfonyl, or lower alkyl sulfonyl.

In accordance with another embodiment of this invention where R³ is cyclopentyl and R⁴ is a mono-substituted pyridine are those compounds where the mono-substituent is $-(CH_2)_n-C(O)-NHR^6$, wherein n and R are as above (Compound I-D4(f)). Among the

Another embodiment of this invention where R^3 is cyclopentyl include compounds where R^4 is unsubstituted pyrimidinyl. The embodiments of those compounds where R^3 is cyclopentyl and R^4 is unsubstituted pyrimidinyl include those compounds where one of R^1 or R^2 is halo, nitro, lower alkyl sulfonyl or perfluoro-lower alkyl and the other is hydrogen or halo.

Another embodiment of this invention includes compounds where R^3 is cyclopentyl where R^4 is an unsubstituted thiadiazolyl ring. Among the embodiments included within those compounds where R^3 is cyclopentyl and R^4 is an unsubstituted thiadiazolyl ring are those compounds wherein one of R^1 or R^2 is halo, nitro, lower alkyl sulfonyl or perfluoro-lower alkyl and the other of said R^1 and R^2 is hydrogen or halo.

In accordance with other embodiments of this invention, R^3 in the compound of formula I can be cycloheptyl or cyclohexyl. The embodiments of the compound of formula I where R^3 is cycloheptyl or cyclohexyl include those compounds where R^4 is thiazolyl which can be mono-substituted or unsubstituted. Embodiments included within such compounds where R^3 is cycloheptyl or cyclohexyl and R^4 is an unsubstituted thiazolyl include those compounds wherein one of R^1 and R^2 is halo, lower alkyl sulfinyl, perfluoro-lower alkyl sulfinyl, perfluoro-lower alkyl or lower alkyl sulfonyl and the other is of said R^1 and R^2 with halo, perfluoro-lower alkyl or hydrogen.

Examples of compounds of formula I according to the present invention, wherein R^4 is a heteroaromatic ring are:

- 2-(3-chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
- 2-(4-bromo-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
- 2-(4-chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethyl-phenyl)-propionamide,
- 3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide,

3-cyclopentyl-2-(3,4-dihydroxy-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(4-methoxy-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide,
4-[2-cyclopentyl-1-(thiazol-2-ylcarbamoyl)-ethyl]-benzoic acid methyl ester,
5 3-cyclopentyl-2-(3-fluoro-4-methoxy-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(3-fluoro-4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-propionamide,
2-(4-chloro-phenyl)-3-cyclopentyl-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide,
10 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide,
3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-methanesulfonyl-phenyl)-
propionamide,
3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-2-(4-methanesulfonyl-phenyl)-
propionamide,
15 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-methyl-thiazol-2-yl)-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-thiazol-2-yl)-propionamide,
{2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid ethyl
ester,
20 {2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid methyl
ester,
2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl
ester,
2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl
ester,
25 {2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid ethyl
ester,
2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl
ester,
30 {2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-yl}-acetic acid ethyl
ester,
{2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid methyl
ester,
{2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid,
35 {2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl
ester,

{2-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-oxo-acetic acid ethyl ester,

3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-nitro-thiazol-2-yl)-propionamide,

3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide,

5 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide,

3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethyl-phenyl)-2-propionamide,

3-cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide,

2-(3-chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

2-(4-amino-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

10 2-(4-cyano-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

2-(4-chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

3-cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide,

2-(4-cyano-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

15 3-cyclopentyl-2-(4-methylsulfanyl-phenyl)-N-pyridin-2-yl-propionamide,

3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethylsulfanyl-phenyl)-propionamide,

3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide,

3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide,

2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

20 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide,

2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,

25 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide,

3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,

3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-carboxymethylpyridin)-2-yl-propionamide,

6-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester,

6-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid,

30 6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,

6-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,

6-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-nicotinic acid methyl ester,

6-[2-(4-amino-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,

3-cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,
 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-(5-methyl-pyridin-2-yl)-propionamide,
 5 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-N-methyl-nicotinamide,
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(1H-imidazol-2-yl)-propionamide,
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-isoxazol-3-yl)-propionamide,
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-oxazol-2-yl-propionamide,
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyridazin-3-yl-propionamide,
 10 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyrimidin-2-yl-propionamide,
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyrimidin-6-yl-propionamide,
 3-cyclopentyl-2-(4-nitro-phenyl)-N-pyrimidin-4-yl-propionamide,
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-[1,3,4]thiadiazol-2-yl-propionamide,
 2-[4-methanesulfonyl phenyl]-3-cyclohexyl N-thiazol-2-yl-propionamide, and
 15 2-[4-methanesulfonyl phenyl]-3-cycloheptyl N-thiazol-2-yl-propionamide.

Examples of compounds of formula I according to the present invention, wherein R⁴ is a residue -C(O)NHR⁴⁰ and R⁴⁰ is as defined above, are:

1-(3-cyclopentyl-2-phenyl-propionyl)-3-methyl-urea,
 20 1-[2-(3-chloro-phenyl)-3 cyclopentyl-propionyl]-3-methyl-urea,
 1-[2-(4-chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,
 1-[2-(4-cyano-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,
 1-[2-(4-bromo-phenyl)-3-cyclopentyl-propionyl]-3-methyl urea,
 [3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,
 25 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,
 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,
 1-allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,
 1-allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea,
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,
 30 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-isopropyl-urea,
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-propyl-urea,

{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester,
{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid methyl ester,
3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid methyl ester,

5 {3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester,
3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic acid ethyl ester,
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-proprionyl]-3-(2-hydroxy-ethyl)-urea,
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-proprionyl]-3-(2-hydroxy-propyl)-urea,

10 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-proprionyl]-3-(3-hydroxy-propyl)-urea,
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-proprionyl]-3-(2-hydroxy-propyl)-urea,
1-(2-chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-proprionyl]-urea, and
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-proprionyl]-3-(3-hydroxy-propyl)-urea.

15 It will be appreciated that the compounds of formula I may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compounds in vivo. Additionally, any physiologically acceptable equivalents of the compounds of formula I, which are capable of producing the parent compounds of formula I in vivo, are within the scope of this invention.

20

The compound of formula I can be prepared starting from the compound of formula V by the following Reaction Scheme:

which is adjacent to the connecting ring carbon atom; said mono-substituted heteroaromatic ring being monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano, -(CH₂)_n-OR⁶, -(CH₂)_n-C(O)OR⁷,
5 -(CH₂)_n-C(O)NHR⁶, -C(O)-C(O)OR⁸ or -(CH₂)_n-NHR⁶, wherein R⁶, R⁷, R⁸ and n are as defined above; R¹⁵ is hydrogen or lower alkyl; and R⁴¹ is lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl or -(CH₂)_n-C(O)OR⁵, wherein R⁵ is hydrogen or lower alkyl and n is as defined above.

The carboxylic acids and their lower alkyl esters of formula V wherein one of R¹ and R² is nitro, cyano, thio, amino, chloro, bromo, or iodo and the other is hydrogen are commercially available. In cases, where only the carboxylic acids are available, they can be converted to the corresponding esters of lower alkyl alcohols using any conventional esterification methods. All the reactions hereto forward are to be carried out on lower alkyl esters of the carboxylic acids of formula V. The amino substituted compounds of
10 formula V can be converted to other substituents either before or after conversion to the compounds of formulae I-a, I-b, I-c or I-d. In this respect, the amino groups can be diazotized to yield the corresponding diazonium compound, which *in situ* can be reacted with the desired lower alkyl thiol, perfluoro-lower alkyl thiol (see for example, Baleja, J.D. *Synth. Comm.* 1984, 14, 215; Giam, C. S.; Kikukawa, K., *J. Chem. Soc. Chem. Comm.* 1980, 756; Kau, D.; Krushniski, J. H.; Robertson, D. W, *J. Labelled Compd Rad.* 1985, 22, 1045; Oade, S.; Shinhama, K.; Kim, Y. H., *Bull Chem Soc. Jpn.* 1980, 53, 2023; Baker, B. R.; et al, *J. Org. Chem.* 1952, 17, 164), or alkaline earth metal cyanide, to yield corresponding compounds of formula V, where one of the substituents is lower alkyl thio, perfluoro-lower alkyl thio, or cyano, and the other is hydrogen. If desired, the
15 lower alkyl thio or perfluoro-lower alkyl thio compounds can then be converted to the corresponding lower alkyl sulfonyl or perfluoro-lower alkyl sulfonyl substituted compounds of formula V by oxidation. Any conventional method of oxidizing alkyl thio substituents to sulfones can be utilized to effect this conversion.

If it is desired to produce compounds of formula V wherein one of R¹ and R² is a
20 lower alkyl or perfluoro-lower alkyl group, the corresponding halo substituted compounds

corresponding compound of formula V where both R¹ and R² are iodine or bromine via a diazotization reaction. Any conventional method of converting amino group to an iodo or bromo group (see for example, Lucas, H. J.; Kennedy, E. R. *Org. Synth. Coll. Vol. II* 1943, 351) can be utilized to effect this conversion. If it is desired to produce compounds 5 of formula V, where both R¹ and R² are lower alkyl thio or perfluoro-lower alkyl thio groups, the compound of formula V where R¹ and R² are amino can be used as starting material. Any conventional method of converting aryl amino group to aryl thioalkyl group can be utilized to effect this conversion. If it is desired to produce compounds of formula 10 V where R¹ and R² are lower alkyl sulfonyl or lower perfluoro alkyl sulfonyl, the corresponding compounds of formula V where R¹ and R² are lower alkyl thio or perfluoro-lower alkyl thio can be used as starting material. Any conventional method of oxidizing alkyl thio substituents to sulfones can be utilized to effect this conversion.

If it is desired to produce compounds of formula V, where both R¹ and R² are substituted with lower alkyl or perfluoro-lower alkyl groups, the corresponding halo 15 substituted compounds of formula V can be used as starting materials. Any conventional method of converting an aromatic halo group to the corresponding alkyl or perfluoro-lower alkyl group can be utilized to effect this conversion.

If it is desired to produce compounds of formula V, where one or both of R¹ and R² are substituted with sulfonamido, the corresponding compounds where one or both of 20 R¹ and R² are substituted with nitro can be used as starting materials. Any standard method of converting a nitrophenyl compound to the corresponding sulfonamidophenyl compound can be used to effect this conversion.

The carboxylic acids corresponding to the compounds of formula V where one of R¹ and R² is nitro and the other is halo are known from the literature (see for 4-chloro-3-25 nitrophenyl acetic acid, Tadayuki, S.; Hiroki, M.; Shinji, U.; Mitsuhiro, S. Japanese patent, JP 71-99504, *Chemical Abstracts* 80:59716; see for 4-nitro-3-chlorophenyl acetic acid, Zhu, J.; Beugelmans, R.; Bourdet, S.; Chastanet, J.; Roussi, G. *J. Org. Chem.* 1995, 60, 6389; Beugelmans, R.; Bourdet, S.; Zhu, J. *Tetrahedron Lett.* 1995, 36, 1279). These carboxylic acids can be converted to the corresponding lower alkyl esters using any

aromatic thio ether group to the corresponding sulfone group can be utilized to effect this conversion.

If it is desired to produce compounds of formula V where one of R¹ and R² is halo and the other is lower alkyl thio or perfluoro-lower alkyl thio, the corresponding 5 compounds where one of R¹ and R² is amino and the other is lower alkyl thio or perfluoro-lower alkyl thio can be used as starting materials. Any conventional method of diazotizing an aromatic amino group and conversion of it *in situ* to an aromatic halide can be utilized to effect this conversion.

If it is desired to produce compounds of formula V where one of R¹ and R² is halo 10 and the other is lower alkyl sulfonyl or perfluoro-lower alkyl sulfonyl, the corresponding compounds where one of R¹ and R² is halo and the other is lower alkyl thio or perfluoro-lower alkyl thio can be used as starting materials. Any conventional method of oxidizing an aromatic thio ether to the corresponding sulfone can be utilized to effect this conversion. If it is desired to produce compounds of various combinations of lower alkyl 15 and perfluoro-lower alkyl groups of compounds of formula V, the corresponding halo substituted compounds of formula V can be used as starting materials. Any conventional method of converting an aromatic halo group to the corresponding alkyl group can be utilized to effect this conversion.

If one wishes to prepare the compound formula V where one of R¹ and R² is nitro 20 and the other is amino, the compound of formula V where one of R¹ and R² is nitro and other is chloro can be used as a starting material. The chloro substituent on the phenyl ring can be converted to an iodo substituent (see for example, Bunnett, J. F.; Conner, R. M.; *Org. Synth. Coll Vol V*, 1973, 478; Clark, J. H.; Jones, C. W. *J. Chem. Soc. Chem. Commun.* 1987, 1409), which in turn can be reacted with an azide transferring agent to 25 form the corresponding azide (see for example, Suzuki, H.; Miyoshi, K.; Shinoda, M. *Bull. Chem. Soc. Jpn.*, 1980, 53, 1765). This azide can then be reduced in a conventional manner to form the amine substituent by reducing it with commonly used reducing agent for converting azides to amines (see for example, Soai, K.; Yokoyama, S.; Ookawa, A. *Synthesis*, 1987, 48).

all of the reactions described to produce various substituents of R¹ and R² in the compound of formula I can also be carried out on the compounds of formulae I-a, I-b I-c or I-d.

5 In the first step of this Reaction Scheme, the alkyl halide of formula VI is reacted with the compound of formula V, to produce the compound of formula VII. In this reaction, if in the compounds of formula V, R¹ or R² is an amino group, such amino group(s) have to be protected before carrying out the alkylation reaction with the alkyl halide of formula VI. The amino group can be protected with any conventional acid
10 removable group (for example, for t-butyloxycarbonyl group see, Bodanszky, M. *Principles of Peptide Chemistry*, Springer -Verlag, New York, 1984, p 99). The protecting group has to be removed from the amino groups after preparing the corresponding amine protected compounds of formulae I-a, I-b, I-c or I-d to obtain the corresponding amines. The compound of formula V is an organic acid having an alpha
15 carbon atom and the compound of formula VI is an alkyl halide so that alkylation occurs at the alpha carbon atom of this carboxylic acid. This reaction is carried out by any conventional means of alkylation of the alpha carbon atom of a lower alkyl ester of a carboxylic acid. Generally, in these alkylation reactions any alkyl halide is reacted with the anion generated from any acetic acid ester. The anion can be generated by using a
20 strong organic base such as lithium diisopropylamide, n-butyl lithium as well as other organic lithium bases. In carrying out this reaction, low boiling ether solvents are utilized such as tetrahydrofuran at low temperatures from -80°C to about -10°C being preferred. However, any temperature from -80°C to room temperature can be used.

25 The compound of formula VII can be converted to the compound of formula XII by any conventional procedure to convert a carboxylic acid ester to an acid. The compound of formula XII can then be condensed with the compound of formula VIII via conventional peptide coupling to produce the compound of formula I-d. In carrying out this reaction, any conventional method of condensing a primary amine with a carboxylic acid can be utilized to effect this conversion. The required amino heteroaromatic

When R⁴¹ is a lower alkenyl group in the compound of formula I-a, this compound can be converted to the corresponding hydroxy lower alkyl group by conventional hydroboration at the olefinic group to produce a corresponding hydroxy group. The hydroxy group, if desired, can be converted to a halo group. Any method of halogenating 5 a hydroxy group can be used in accordance with this invention.

On the other hand, if it is desired to produce the compound of formula I-b the compound of formula XII is first converted to the methyl ester of formula XI, and thereafter reacted with urea to produce the compound of formula I-b. This reaction is carried out by utilizing any conventional means of reacting a methyl ester with urea to 10 form the corresponding condensation product.

The compound of formula I-c, i.e. the compound of formula I wherein R⁴-C(O)NHR⁴⁰ and R⁴⁰ is -CO-(CH₂)_n-C(O)OR⁶, is produced from the monoacid chloride XIII of the monoester of the corresponding dicarboxylic acid. The monoacid chloride XIII is coupled with the compounds of formula I-b using standard coupling methods.

15 The compound of formula VII has an asymmetric carbon atom through which the group -CH₂R³ and the acid amide substituents are connected. In accordance with this invention, the preferred stereoconfiguration of this group is R.

If it is desired to produce the R or the S isomer of the compound of formula I, this compound can be separated into these isomers by any conventional chemical means. 20 Among the preferred chemical means is to react the compound of formula XII with an optically active base. Any conventional optically active base can be utilized to carry out this resolution. Among the preferred optically active bases are the optically active amine bases such as alpha-methylbenzylamine, quinine, dehydroabietylamine and alpha-methylnaphthylamine. Any of the conventional techniques utilized in resolving organic 25 acids with optically active organic amine bases can be utilized in carrying out this reaction.

In the resolution step, the compound of formula XII is reacted with the optically active base in an inert organic solvent medium to produce salts of the optically active amine with both the R and S isomers of the compound of formula XII. In the formation

The following compounds were tested and found to have excellent glucokinase activator *in vivo* activity when administered orally in accordance with the assay described in Example B:

- 3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide;
- 5 3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethoxy-phenyl)-propionamide;
- 3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide;
- 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide;
- 6-[3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester;
- 10 N-(5-Chloro-pyridin-2-yl)-3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide;
- 3-Cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide;
- 3-Cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide;
- 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl) propionamide;
- 15 6-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester;
- 3-Cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide;
- 3-Cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide;
- 20 2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide;
- 2-(3-Cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide;
- 2-(4-Chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide;
- 2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide;
- N-(5-Bromo-pyridin-2-yl)-2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-25 propionamide;
- 2-[3-Chloro-4-methanesulfonyl-phenyl]-3-cyclopentyl-N-thiazol-2-yl-propionamide;
- (2R)-3-Cyclopentyl-2-(4-methanesulfonylphenyl)-N-thiazol-2-yl-propionamide;
- 2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide;
- 2-(3-Cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide;
- 30 3-Cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide;
- 3-Cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide; and
- N-(5-Bromo-pyridin-2-yl)-2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-28 propionamide.

acid or salts thereof. Suitable excipients for use with soft gelatine capsules include for example vegetable oils, waxes, fats, semi-solid or liquid polyols etc.; according to the nature of the active ingredients it may however be the case that no excipient is needed at all for soft gelatine capsules. For the preparation of solutions and syrups, excipients which may be used include for example water, polyols, saccharose, invert sugar and glucose. For injectable solutions, excipients which may be used include for example water, alcohols, polyols, glycerine, and vegetable oils. For suppositories, and local or percutaneous application, excipients which may be used include for example natural or hardened oils, waxes, fats and semi-solid or liquid polyols.

10

The pharmaceutical compositions may also contain preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, salts for the variation of osmotic pressure, buffers, coating agents or antioxidants. As mentioned earlier, they may also contain other therapeutically valuable agents. It is a prerequisite that all adjuvants used in the manufacture of the preparations are non-toxic.

Preferred forms of use are intravenous, intramuscular or oral administration, most preferred is oral administration. The dosages in which the compounds of formula (I) are administered in effective amounts depend on the nature of the specific active ingredient, the age and the requirements of the patient and the mode of application. In general, dosages of about 1-100 mg/kg body weight per day come into consideration.

This invention will be better understood from the following examples, which are for purpose of illustration and are not intended to limit the invention defined in the claims that follow thereafter.

thiazol-5-yl}-oxo-acetic acid ethyl ester as a white solid: mp 129-131°C; FAB-HRMS m/e calcd for $C_{21}H_{22}Cl_2N_2O_4S$ ($M+H$)⁺ 469.0755, found 469.0765.

(c) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and (2-amino-thiazol-4-yl)-acetic acid ethyl ester: {2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester as a yellow solid: mp 138-139°C; FAB-HRMS m/e calcd for $C_{21}H_{24}Cl_2N_2O_3S$ ($M+H$)⁺ 455.0963, found 455.0960.

5 (d) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-5-methylthiazole: 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-thiazol-2-yl)-propionamide as a white solid: mp 142-143°C; EI-HRMS m/e calcd for $C_{18}H_{20}Cl_2N_2OS$ 10 (M^+) 382.0673, found 382.0679.

(e) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-4-methylthiazole: 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-methyl-thiazol-2-yl)-propionamide as a white foam: mp 151-152°C; FAB-HRMS m/e calcd for $C_{18}H_{20}Cl_2N_2OS$ ($M+H$)⁺ 383.0751, found 383.0758.

15 (f) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-thiazole-4-carboxylic acid ethyl ester: 2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a white solid: mp 104-107°C; FAB-HRMS m/e calcd for $C_{20}H_{22}Cl_2N_2O_3S$ ($M+H$)⁺ 441.0807, found 441.0808.

(g) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-thiazole-5-carboxylic acid ethyl ester: 2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-5-carboxylic acid ethyl ester as a light yellow solid: mp 136-137°C; FAB-HRMS m/e calcd for $C_{20}H_{22}Cl_2N_2O_3S$ ($M+H$)⁺ 441.0807, found 441.0803.

20 (h) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-5-nitrothiazole: 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-nitro-thiazol-2-yl)-propionamide as an orange solid: mp 67-71°C; FAB-HRMS m/e calcd for $C_{17}H_{17}Cl_2N_3O_3S$ ($M+H$)⁺ 414.0446, found 414.0442.

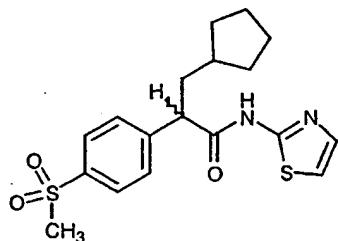
25 (i) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-thiazole-4-carboxylic acid amide: 2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-

A solution of 2-(4-bromo-phenyl)-3-cyclopentyl-propionic acid (1.01 g, 3.39 mmol) in methylene chloride (8.5 mL) was treated with 2 drops of dry *N,N*-dimethylformamide. The reaction mixture was cooled to 0°C and then treated with oxalyl chloride (3 mL, 33.98 mmol). The reaction mixture was stirred at 0°C for 10 min and then stirred at 25°C 5 for 15 h. The reaction mixture was concentrated *in vacuo*. The resulting yellow oil was dissolved in a small amount of methylene chloride and slowly added to a cooled solution (0°C) of 2-aminothiazole (680.6 mg, 6.79 mmol) and *N,N*-diisopropylethylamine (1.2 mL, 6.79 mmol) in methylene chloride (17 mL). The resulting reaction mixture was stirred at 0°C for 10 min and then at 25°C for 15 h. The reaction mixture was 10 concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a 10% aqueous hydrochloric acid solution (2 x 100 mL), washed with a saturated aqueous sodium bicarbonate solution (2 x 100 mL), and washed with a saturated aqueous sodium chloride solution (1 x 100 mL). The organic layer was then dried over sodium sulfate, filtered, and 15 concentrated *in vacuo* to afford 2-(4-bromo-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (1.23 g, 95%) as an orange solid which was used in subsequent reactions without further purification. An analytical sample was recrystallized from ethyl acetate to provide a cream solid: mp 201-202°C; EI-HRMS m/e calcd for C₁₇H₁₉BrN₂OS (M⁺) 378.0401, found 378.0405.

20

Example 3

(A) 3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide



allowed to warm to 25°C over 30 min. The brown reaction mixture was then treated with 2-aminothiazole (4.98 g, 49.69 mmol). The resulting reaction mixture was stirred at 25°C for 19 h. The reaction mixture was then concentrated *in vacuo* to remove methylene chloride. The remaining black residue was diluted with a 10% aqueous hydrochloric acid solution (400 mL) and then extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate then 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide (4.49 g, 72%) as a white solid: mp 216-217°C; EI-HRMS m/e calcd for C₁₈H₂₂N₂O₃S₂ (M⁺) 378.1072, found 378.1071.

(B) In an analogous manner, there were obtained:

- (a) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and 2-aminothiazole-4-carboxylic acid methyl ester: 2-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester as a tan solid: mp 126-128°C; EI-HRMS m/e calcd for C₂₀H₂₄N₂O₅S₂ (M⁺) 436.1127, found 436.1119.
- (b) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and 2-aminothiazole-4-carboxylic acid ethyl ester: 2-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a light yellow solid: mp 101-103°C; EI-HRMS m/e calcd for C₂₁H₂₆N₂O₅S₂ (M⁺) 450.1283, found 450.1284.
- (c) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and methyl 2-amino-4-thiazoleacetate: {2-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester as a yellow solid: mp 63-65°C; EI-HRMS m/e calcd for C₂₁H₂₆N₂O₅S₂ (M⁺) 450.1283, found 450.1294.
- (d) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and ethyl 2-amino-4-thiazoleacetate: {2-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-

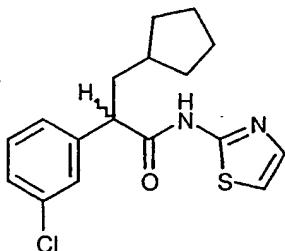
h. The reaction was then concentrated *in vacuo*. The residue was dissolved in methylene chloride (50 mL) and washed with a saturated aqueous sodium bicarbonate solution (2 x 25 mL), water (1 x 50 mL), and a saturated aqueous sodium chloride solution (1 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give (4-nitro-phenyl)-acetic acid methyl ester (5.27 g, 97.9%) as a pale yellow solid: mp 29-30°C; EI-HRMS m/e calcd for C₉H₉NO₄ (M⁺) 195.0531, found 195.0532.

5 A solution of freshly prepared lithium diisopropylamide (43.3 mL of a 0.3M stock solution, 12.99 mmol) cooled to -78°C was treated with (3-nitro-phenyl)-acetic acid methyl ester (2.45 g, 12.56 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (32 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. Iodomethylcyclopentane (2.78 g, 13.23 mmol) was then added in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.78 mL), and the mixture was stirred at -78°C for 3 h.

10 The reaction was warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (25 mL) and was concentrated *in vacuo*. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were washed with a saturated aqueous lithium chloride solution (2 x 25 mL), dried over sodium sulfate, 15 filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid methyl ester (1.63 g, 46.8%) as pale yellow oil: EI-HRMS m/e calcd for C₁₅H₁₉NO₄ (M⁺) 277.1314, found 277.1317.

20

25 A solution of 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid methyl ester (0.55 g, 2.0 mmol) in tetrahydrofuran/water (10 mL, 3:1) was treated with lithium hydroxide (185 mg, 4.40 mmol). The reaction was stirred at 25°C for 48 h. The tetrahydrofuran was then removed *in vacuo*. The residue was diluted with water (25 mL) and extracted with ether (1 x 20 mL). The aqueous layer was acidified to pH = 2 with a 3N aqueous hydrochloric

Example 6**2-(3-Chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide**

(3-Chloro-phenyl)-acetic acid (6.03 g, 0.03 mol) was dissolved in ethanol (37.7 mL) and
5 treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for
12 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel
60, .230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3-chloro-phenyl)-acetic acid
ethyl ester (6.10 g, 86.8%) as a clear oil: EI-HRMS m/e calcd for C₁₀H₁₁ClO₂ (M⁺)
198.0448, found 198.0442.

10

A solution of freshly prepared lithium diisopropylamide (23 mL of 0.31M stock solution,
7.13 mmol) cooled to -78°C was treated with (3-chloro-phenyl)-acetic acid ethyl ester
(1.28 g, 6.48 mmol) in tetrahydrofuran/hexamethylphosphoramide (16.1 mL, 3:1). The
resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated
15 with a solution of iodomethylcyclopentane (1.50 g, 7.13 mmol) in
hexamethylphosphoramide (1 mL). The reaction mixture was stirred at -78°C for 4 h.
The reaction was warmed to 25°C and stirred at 25°C for 16 h. The reaction mixture was
then quenched by the dropwise addition of a saturated aqueous ammonium chloride
solution (20 mL). This mixture was poured into water (100 mL) and extracted with ethyl
acetate (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and
concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25
hexanes/ethyl acetate) afforded 2-(3-chloro-phenyl)-3-cyclopentyl-propionic acid ethyl
ester (1.70 g, 93%) as a yellow oil: EI-HRMS m/e calcd for C₁₆H₂₁ClO₂ (M⁺) 280.1230,
found 280.1238.

60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (4-chloro-phenyl)-acetic acid ethyl ester (6.45 g, 88%) as a pale yellow solid: mp 39-41°C; EI-HRMS m/e calcd for $C_{10}H_{11}ClO_2 (M^+)$ 198.0448, found 198.0452.

5 A solution of freshly prepared lithium diisopropylamide (23.0 mL of 0.31M stock solution, 7.13 mmol) cooled to -78°C was treated with (4-chloro-phenyl)-acetic acid ethyl ester (1.28 g, 6.48 mmol) in tetrahydrofuran/hexamethylphosphoramide (16.1 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.50 mg, 7.13 mmol) in
10 hexamethylphosphoramide (1 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was warmed to 25°C and stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (20 mL). This mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and
15 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid ethyl ester (1.65 g, 90.9%) as a yellow oil: EI-HRMS m/e calcd for $C_{16}H_{21}Cl_2O_2 (M^+)$ 280.1230, found 280.1227.

20 A mixture of 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid ethyl ester (1.65 g, 5.89 mmol) and methyl urea (654 mg, 8.83 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 16.9 mL, 11.78 mmol) was refluxed at 100°C for 6 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 1-[2-(4-chloro-phenyl)-3-
25 cyclopentyl-propionyl]-3-methyl-urea (105.3 mg, 5.8 %) as a white solid: mp 145-147°C; EI-HRMS m/e calcd for $C_{16}H_{21}ClN_2O_2 (M^+)$ 308.1292, found 308.1291. The methyl ester of the starting material was recovered from the reaction mixture due to transesterification.

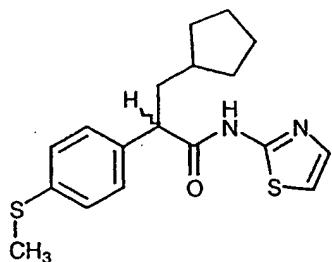
(634.9 mg, 65%) as a white solid: mp 94-95°C; EI-HRMS m/e calcd for C₁₅H₁₇F₃O₂ (M⁺) 309.1079, found 309.1072.

A solution of 3-cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionic acid (185 mg, 0.64 mmol) in methylene chloride (6.5 mL) was cooled to 0°C and was treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.35 mL, 0.71 mmol) and a few drops of N,N-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and at 25°C for 30 min. The reaction mixture was then treated with a solution of 2-aminothiazole (142 mg, 1.42 mmol) in tetrahydrofuran (3.23 mL) and N,N-diisopropylethylamine (0.27 mL, 1.55 mmol). The solution was stirred at 25°C for 5 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethyl-phenyl)-propionamide (127 mg, 53.3%) as a white solid: mp 210-212°C; EI-HRMS m/e calcd for C₁₈H₁₉F₃N₂OS (M⁺) 368.1175, found 368.1170.

15

Example 9

3-Cyclopentyl-2-(4-methylsulfanyl-phenyl)-N-thiazol-2-yl-propionamide

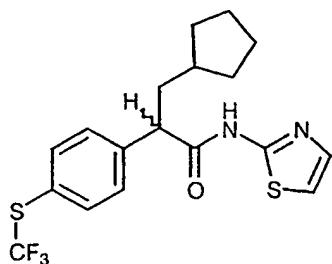


A solution of diisopropylamine (3.2 mL, 23.16 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (2.3 mL, 23.16 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(methylthio)phenylacetic acid (2.01 g, 11.03

propionamide (114 mg, 44%) as a white solid: mp 195-196°C; EI-HRMS m/e calcd for C₁₈H₂₂N₂OS₂ (M⁺) 346.1174, found 346.1171.

Example 10

5 **3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethylsulfanyl-phenyl)-propionamide**



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount 10 of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (300 mL). The organic layer was washed with a saturated aqueous 15 sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.47 g, 58%) as a cream solid: mp 69-71°C; EI-HRMS m/e calcd for C₁₅H₁₇F₃O₂S (M⁺) 318.0901, found 318.0912.

mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at 5 which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted 10 with ethyl acetate (300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.47 g, 58%) as a cream solid: mp 69-71°C; EI-HRMS m/e calcd 15 for C₁₅H₁₇F₃O₂S (M⁺) 318.0901, found 318.0912.

A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.33 g, 4.18 mmol) in methanol (10 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The resulting reaction mixture was heated under reflux for 36 h. The reaction 20 mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 97/3 25 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.37 g, 99%) as a light yellow oil: EI-HRMS m/e calcd for C₁₆H₁₉F₃O₂S (M⁺) 332.1058, found 332.1052.

A solution of 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid (164.0 mg, 0.47 mmol) and triphenylphosphine (184.2 mg, 0.70 mmol) in methylene chloride (1.2 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (141.6 mg, 0.80 mmol) in small portions. After the complete addition of *N*-bromosuccinimide, the 5 reaction mixture was allowed to warm to 25°C where it was stirred for 1 h. The reaction mixture was then treated with 2-aminothiazole (140.6 mg, 1.40 mmol). The resulting reaction mixture was stirred at 25°C for 22 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide (47.9 mg, 24%) as a cream solid: mp 10 189-191°C; EI-HRMS m/e calcd for C₁₈H₁₉F₃N₂O₃S₂ (M⁺) 432.0789, found 432.0791.

(B) In an analogous manner, there were obtained:

(a) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and 2-aminothiazole-4-carboxylic acid methyl ester: 2-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester as a gray solid: mp 122-125°C; EI-HRMS m/e calcd for C₂₀H₂₁F₃N₂O₅S₂ (M⁺) 490.0844, found 490.0844.

(b) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and 2-aminothiazole-4-carboxylic acid ethyl ester: 2-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a white solid: mp 132-134°C; EI-HRMS m/e calcd for C₂₁H₂₃F₃N₂O₅S₂ (M⁺) 504.1000, found 504.0988.

(c) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and methyl 2-amino-4-thiazoleacetate: {2-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester as a yellow foam: mp 48-52°C; EI-HRMS m/e calcd for C₂₁H₂₃F₃N₂O₅S₂ (M⁺) 504.1000, found 504.0998.

mesh, 9/1 then 4/1 hexanes/ethyl acetate) afforded (3-chloro-4-methylsulfanyl-phenyl)-hydroxy-acetic acid ethyl ester (1.43 g, 38%) as a white solid: mp 56-57°C; EI-HRMS m/e calcd for $C_{11}H_{13}ClO_3S$ (M^+) 260.0273, found 260.0276.

5 A solution of (3-chloro-4-methylsulfanyl-phenyl)-hydroxy-acetic acid ethyl ester (1.43 g, 5.49 mmol) in pyridine (2 mL) was treated with acetic anhydride (2 mL) and 4-dimethylaminopyridine (50 mg, 0.41 mmol). The reaction mixture was stirred at 25°C for 16 h. The reaction mixture was then diluted with methylene chloride (100 mL). The organic layer was washed with a 1N aqueous hydrochloric acid solution (2 x 30 mL),
10 washed with a saturated aqueous sodium chloride solution (1 x 30 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded acetoxy-(3-chloro-4-methylsulfanyl-phenyl)-acetic acid ethyl ester (1.51 g, 91%) as a light yellow oil: EI-HRMS m/e calcd for $C_{13}H_{15}ClO_4S$ (M^+) 302.0379, found 302.0387.

15

A solution of acetoxy-(3-chloro-4-methylsulfanyl-phenyl)-acetic acid ethyl ester (1.47 g, 4.87 mmol) in hexamethylphosphoramide (7.2 mL) and methanol (20 μ L) was treated with a 0.1M solution of samarium iodide in tetrahydrofuran (146 mL, 14.6 mmol). The reaction mixture was stirred at 25°C under nitrogen for 6 min. During this time period,
20 the reaction mixture changed from purple to white. The reaction mixture was diluted with water (150 mL) and then extracted with methylene chloride (3 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded (3-chloro-4-methylsulfanyl-phenyl)-acetic acid ethyl ester (0.71 g, 60%)
25 as a light yellow oil: EI-HRMS m/e calcd for $C_{11}H_{13}ClO_2S$ (M^+) 244.0324, found 244.0332.

A solution of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.62 g, 1.41 mmol) and 2-(3-chloro-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid (0.29 g, 0.95 mmol) in methylene chloride (10 mL) was treated with *N,N*-diisopropylethylamine (500 μ L, 2.87 mmol) and 2-aminothiazole (140 mg, 1.27mmol).

5 The mixture was stirred under nitrogen at 25°C for 14 h. The reaction mixture was then washed with a 6N aqueous hydrochloric acid solution (1 x 15 mL) and washed with a saturated aqueous sodium chloride solution (1 x 25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(3-chloro-4-
10 methylsulfanyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (0.26 g, 71%) as a white solid: EI-HRMS m/e calcd for $C_{18}H_{21}ClN_2OS_2(M^+)$ 380.0783, found 380.0792.

A solution of 2-(3-chloro-4-methylsulfanyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (187 mg, 0.49 mmol) in methylene chloride (10 mL) was cooled to 0°C
15 under nitrogen and then treated with 3-chloroperoxybenzoic acid (456. 8 mg based on 50% purity). The reaction mixture was stirred for 3 h, and during this period, the temperature was allowed to warm to 25°C. The reaction mixture was then diluted with methylene chloride (50 mL). The organic layer was washed with a saturated aqueous sodium carbonate solution (1 x 20 mL), washed with a saturated aqueous sodium chloride
20 solution (1 x 20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (102 mg, 50%) as a white solid: EI-HRMS m/e calcd for $C_{18}H_{21}ClN_2O_3S_2(M^+)$ 412.0682, found 412.0674.

mol) in a small amount of dry tetrahydrofuran was added slowly. The reaction mixture was then stirred at -78°C for 50 min, and then allowed to warm to 25°C, where it was stirred for 36 h. The reaction mixture was quenched with water (100 mL), and the resulting reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The 5 remaining residue was diluted with ethyl acetate (1.5 L). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 500 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid methyl ester (41.79 g, 68%) as a yellow viscous 10 oil: EI-HRMS m/e calcd for C₁₆H₂₂O₄S (M⁺) 310.1239, found 310.1230.

A solution of 3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid methyl ester (50.96 g, 0.16 mol) in methanol (410 mL) was treated with a 1N aqueous sodium hydroxide solution (345 mL, 0.35 mol). The reaction mixture was stirred at 25°C for 24 15 h. The reaction mixture was concentrated *in vacuo* to remove methanol. The resulting aqueous residue was acidified to pH = 2 with concentrated hydrochloric acid and then extracted with ethyl acetate (5 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford pure 3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid (43.61 g, 90%) as a white solid which was used 20 without further purification: mp 152-154°C; EI-HRMS m/e calcd for C₁₅H₂₀O₄S (M⁺) 296.1082, found 296.1080.

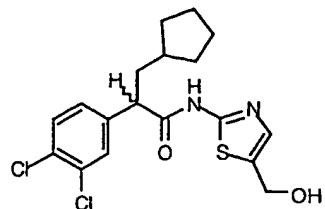
Two separate reactions were setup in parallel: (1) A solution of (R)-(+)-4-benzyl-2-oxazolidinone (3.67 g, 20.73 mmol) in dry tetrahydrofuran (35 mL) was cooled to -78°C 25 and then treated with a 2.5M solution of *n*-butyllithium in hexanes (7.9 mL, 19.86 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then allowed to warm to 25°C, where it was stirred for 1.5 h. (2) A solution of racemic 3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid (5.12 g, 17.27 mmol) in dry tetrahydrofuran (35 mL) was cooled to 0°C and then treated with triethylamine (2.8 mL, 19.86 mmol). The

methanesulfonylphenyl)propionyl]-oxazolidin-2-one (3.84 g, 8.43 mmol) in tetrahydrofuran (33 mL) and water (11 mL). The reaction mixture was stirred 0°C for 1.5 h. The reaction mixture was then quenched with a 1.5N aqueous sodium sulfite solution (25 mL). The reaction mixture was further diluted with water (300 mL). The resulting aqueous layer was continuously extracted with diethyl ether until thin layer chromatography indicated the absence of the recovered chiral oxazolidinone in the aqueous layer. The aqueous layer was then acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and extracted with ethyl acetate (300 mL). The organic extract was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (2R)-3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid as a white solid (2.23 g, 89%) which was used without further purification. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 30/1 methylene chloride/methanol then 10/1 methylene chloride/methanol) was used to obtain a purified sample for analytical data and afforded pure (2R)-3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid as a white foam: mp 62-64°C (foam to gel); $[\alpha]^{23}_{589} = -50.0^\circ$ ($c=0.02$, chloroform); EI-HRMS m/e calcd for $C_{15}H_{20}O_4S$ (M^+) 296.1082, found 296.1080.

A solution of triphenylphosphine (3.35 g, 12.79 mmol) in methylene chloride (19 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (2.28 g, 12.79 mmol) in small portions. The reaction mixture was stirred at 0°C for 30 min, and during this time period, the color of the reaction mixture changed from light yellow to a darker yellow then to a purple color. The cooled purple reaction mixture was then treated with the (2R)-3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid (2.23 g, 7.52 mmol). The resulting reaction mixture was then allowed to warm to 25°C over 45 min, at which time, the reaction mixture was then treated with 2-aminothiazole (1.88 g, 18.81 mmol). The resulting reaction mixture was stirred at 25°C for 12 h. The reaction mixture was then concentrated *in vacuo* to remove methylene chloride. The remaining black residue was diluted with ethyl acetate (300 mL) and then washed well with a 10% aqueous hydrochloric acid solution (2 x 100 mL), a 5% aqueous sodium bicarbonate solution (3 x

20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min period. The reaction mixture turned deep purple (almost black) in color. The reaction mixture was then stirred at -78°C for 1 h, at which time, a solution of 5 iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was then stirred at -78°C and then allowed to warm to 25°C, where it was stirred for 48 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (50 mL), and the resulting reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue 10 was diluted with ethyl acetate (150 mL) and water (50 mL). The organic phase was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (2.17 g, 32%) as a yellow oil: EI-HRMS m/e calcd for 15 C₁₅H₁₈ClNO₄ (M⁺) 311.0924, found 311.0927.

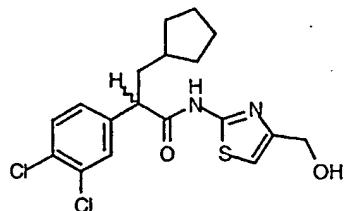
A solution of 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (1.00 g, 3.21 mmol) and sodium methanesulfinate (0.36 g, 3.53 mmol) in dimethyl sulfoxide (3 mL) was heated at 130°C for 5 h. The black reaction mixture was then poured over ice 20 (20 g), resulting in the formation of a brown sticky substance. The resulting mixture was then treated with ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck 25 Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (0.95 g, 84%) as a yellow gel: FAB-HRMS m/e calcd for C₁₆H₂₁NO₆S (M+H)⁺ 356.1169, found 356.1175.

Example 15**3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide**

5 A solution of 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-5-carboxylic acid ethyl ester (prepared in Example 1 (B)(g), 110 mg, 0.25 mmol) in diethyl ether (2 mL) at 0°C was slowly treated with lithium aluminum hydride (12 mg, 0.31 mmol). The resulting reaction mixture continued to stir at 0°C and was allowed to gradually warm to 25°C. The reaction mixture was then stirred at 25°C over a period of 10 14 h. The reaction mixture was slowly quenched by the dropwise addition of water (5 mL). The resulting reaction mixture was partitioned between water and ethyl acetate. A saturated aqueous sodium chloride solution was added to break up the emulsions. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ethyl acetate) 15 afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide (52.9 mg, 53%) as a light yellow solid: mp 128-130°C; EI-HRMS m/e calcd for C₁₈H₂₀Cl₂N₂O₂S (M⁺) 398.0623, found 398.0623.

Example 17

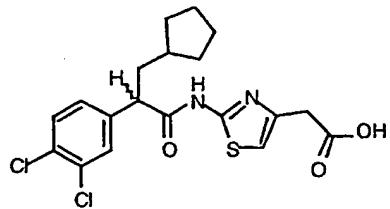
3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide



5 A solution of 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 1(B)(f), 200 mg, 0.45 mmol) in tetrahydrofuran (3 mL) at 25°C was slowly treated with sodium borohydride (26.0 mg, 0.68 mmol). The reaction mixture was heated under reflux for 48 h. The reaction mixture was allowed to cool to 25°C and then slowly quenched by the dropwise addition
10 of water. The resulting reaction mixture was partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide (44.9 mg, 25%) as a white solid: mp 88-90°C; EI-HRMS m/e calcd for
15 C₁₈H₂₀Cl₂N₂O₂S (M⁺) 398.0623, found 398.0631.

Example 18

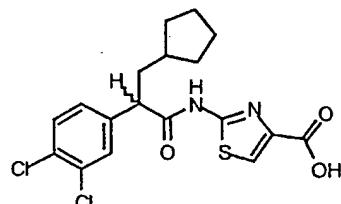
{2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid



propionylamino]-thiazole-5-carboxylic acid (210 mg, 22%) as a white solid: mp 269-270°C; FAB-HRMS m/e calcd for $C_{18}H_{18}Cl_2N_2O_3S$ ($M+H$)⁺ 413.0493, found 413.0483.

Example 20

5 2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid

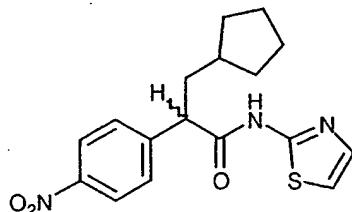


A solution of 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 1(B)(f), 600 mg, 1.36 mmol) in absolute ethanol (6 mL) was treated with a 1N aqueous sodium hydroxide solution (2.85 mL, 2.85 mmol). The reaction mixture was heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove absolute ethanol. The resulting yellow residue was acidified to pH = 2 with concentrated hydrochloric acid and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Precipitation from 1/1 hexanes/ethyl acetate afforded 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid (399 mg, 71%) as a white solid: mp 285-287°C; FAB-HRMS m/e calcd for $C_{18}H_{18}Cl_2N_2O_3S$ ($M+H$)⁺ 413.0493, found 413.0481.

propionylamino]-thiazole-5-carboxylic acid methyl ester as a white solid: mp 150-151°C; FAB-HRMS m/e calcd for C₁₉H₂₀Cl₂N₂O₃S (M+H)⁺ 427.0650, found 427.0650.

Example 22

5 (A) 3-Cyclopentyl-2-(4-nitro-phenyl)-N-thiazol-2-yl-propionamide

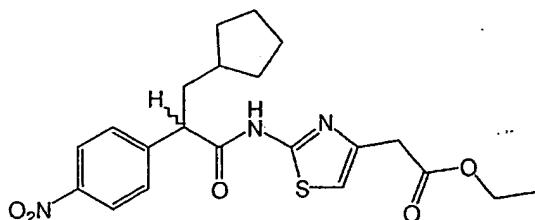


A solution of freshly prepared lithium diisopropylamide (430.55 mL of a 0.3M stock solution, 129.16 mmol) cooled to -78°C was treated with (4-nitro-phenyl)-acetic acid ethyl ester (26.32 g, 125.83 mmol) in tetrahydrofuran/hexamethylphosphoramide (312.5 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. Iodomethylcyclopentane (27.75 g, 132.1 mmol) was then added in hexamethylphosphoramide (27.75 mL). The mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (250 mL). This mixture was concentrated, diluted with water (250 mL), and extracted with ethyl acetate (3 x 300 mL). The organics were washed with a saturated aqueous lithium chloride solution (2 x 250 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 98/2 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (28.30 g, 77.2%) as a yellow oil: EI-HRMS m/e calcd for C₁₆H₂₁NO₄ (M⁺) 291.1470, found 291.1470.

A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (14.1 g, 48.06 mmol) in tetrahydrofuran/water (300 mL, 3:1) was treated with lithium hydroxide (4.35 g,

Example 23

{2-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester



5 A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid (prepared in Example 22A, 263.0 mg, 1.0 mmol) in *N,N*-dimethylformamide (10 mL) was treated with *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (379 mg, 1.0 mmol), (2-amino-thiazol-4-yl)-acetic acid ethyl ester (279 mg, 1.5 mmol) and *N,N*-diisopropylethylamine (0.34 mL, 2.0 mmol). The reaction mixture was stirred at 25°C for

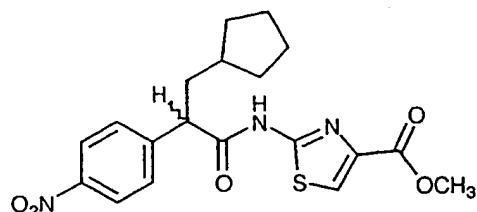
10 5 h. The reaction mixture was then poured into a 2N aqueous hydrochloric acid solution (25 mL) and extracted with ethyl acetate (3 x 25 mL). The organic layers were combined and washed with water (1 x 75 mL), a saturated aqueous sodium bicarbonate solution (1 x 75 mL), a saturated aqueous sodium chloride solution (3 x 75 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 15 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded {2-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester (70.0 mg, 39.4%) as a pale yellow oil: FAB-HRMS m/e calcd for C₂₁H₂₅N₃O₅S (M+H)⁺ 432.1593, found 432.1595.

under hydrogen gas at 60 psi at 25°C for 4 h. The catalyst was then filtered off through a pad of celite (ethyl acetate). The filtrate was concentrated *in vacuo* to give {2-[2-(4-amino-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid methyl ester (64.5 mg, 93.3%) as a tan oil: EI-HRMS m/e calcd for C₂₀H₂₅N₃O₃S (M⁺) 387.1616, found 387.1612.

Example 26

**2-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazole-4-carboxylic acid
methyl ester**

10



A solution of 2-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 39(B)(b), 135 mg, 0.32 mmol) in methanol (10 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 68 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 2-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester (71.4 mg, 54.8%) as a pale yellow solid: EI-HRMS m/e calcd for C₁₉H₂₁N₃O₅S (M⁺) 403.1201, found 403.1188.

(49.7 mL, 3:1). The resulting reaction solution was stirred at -78°C for 1 h. Iodomethylcyclopentane (4.64 g, 22.08 mmol) was then added in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (4.64 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 48 h. The
5 solution was then quenched by the slow addition of the reaction mixture to a 2N aqueous hydrochloric acid solution (50 mL). The product was extracted into ethyl acetate (1 x 150 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 85/15 hexanes/ethyl acetate) afforded 2-(3-chloro-phenyl)-3-cyclopentyl-propionic acid (3.68 g, 72.9%) as a yellow
10 solid: mp 70-72°C; EI-HRMS m/e calcd for C₁₄H₁₇ClO₂ (M⁺) 252.0917, found 252.0915.

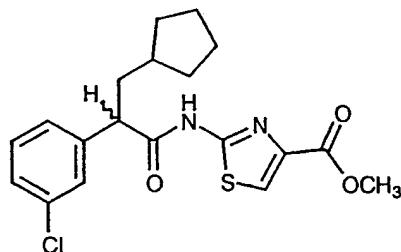
A solution of 2-(3-chloro-phenyl)-3-cyclopentyl-propionic acid (252 mg, 1.0 mmol) in methylene chloride (10 mL) was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few drops of N,N-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min and at 25°C for 2 h. The reaction mixture was then treated with (2-amino-thiazol-4-yl)-acetic acid ethyl ester (409 mg, 2.2 mmol) and N,N-diisopropylethylamine (0.5 mL, 2.4 mmol). This
15 solution was stirred at 25°C for 48 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded {2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester (254 mg, 60.3%) as a white solid: mp 121-125°C; EI-HRMS m/e calcd for C₂₁H₂₅ClN₂O₃S (M⁺) 420.1274, found 420.1268.

(B) In an analogous manner, there were obtained:

25 (a) From 2-amino-thiazole-4-carboxylic acid ethyl ester and 2-(3-chloro-phenyl)-3-cyclopentyl-propionic acid: 2-[2-(3-Chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a white solid: mp 167-168°C; EI-HRMS m/e calcd for C₂₀H₂₃ClN₂O₃S (M⁺) 406.1117, found 406.1103.

Example 30

2-[2-(3-Chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl ester

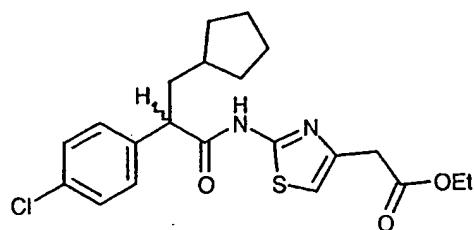


5 A solution of 2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 28(B)(a), 94.5 mg, 0.23 mmol) in methanol (15 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 40 h. The reaction was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate)

10 afforded 2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl ester (36.8 mg, 40.3%) as a white solid: mp 95-98°C; EI-HRMS m/e calcd for C₁₉H₂₁ClN₂O₃S (M⁺) 392.0961, found 392.0989.

Example 31

15 (A) {2-[2-(4-Chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester



A solution of freshly prepared lithium diisopropylamide (78.0 mL of a 0.91M stock solution, 70.98 mmol) cooled to -78°C was treated with (4-chloro-phenyl)-acetic acid

thiazole-4-carboxylic acid ethyl ester as a white solid: mp 114-116°C; EI-HRMS m/e calcd for $C_{20}H_{23}ClN_2O_3S$ (M^+) 406.1117, found 406.1119.

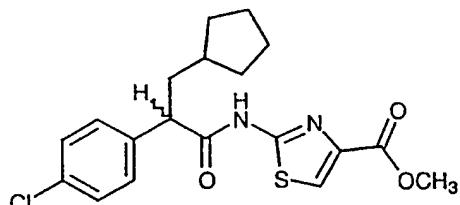
(b) From 2-amino-pyridine and 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid: 2-(4-Chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide as a clear oil: EI-HRMS m/e 5 calcd for $C_{19}H_{21}ClN_2O$ (M^+) 328.1342, found 328.1355.

(c) From 6-amino-nicotinic acid methyl ester and 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid: 6-[2-(4-Chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester as a white foam: EI-HRMS m/e calcd for $C_{21}H_{23}ClN_2O_3$ (M^+) 386.1397, found 386.1384.

10

Example 32

2-[2-(4-Chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl ester:

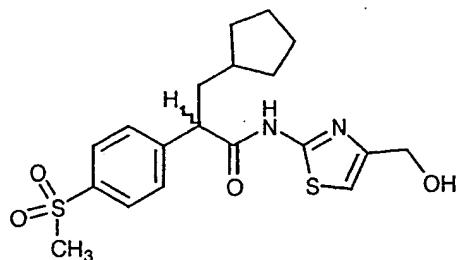


15 A solution of 2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 31(B)(a), 105 mg, 0.25 mmol) in methanol (10 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 68 h. The reaction was concentrated *in vacuo*. High pressure liquid chromatography (ChromegaspHERE SI-60, 10 µm, 60 Å, 25 cm X 23 cm ID, 75/25 20 heptane/ethyl acetate) afforded 2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl ester (41.3 mg, 40.7%) as a white solid: mp 156-157°C; EI-HRMS m/e calcd for $C_{19}H_{21}ClN_2O_3S$ (M^+) 392.0961, found 392.0956.

for 2 h. The reaction was then quenched by the dropwise addition of water. The reaction was then diluted with more water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) 5 afforded 2-(4-chloro-phenyl)-3-cyclopentyl-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide (63.4 mg, 55.4%) as a white solid: mp 115-117°C; EI-HRMS m/e calcd for C₁₈H₂₁ClN₂O₂S (M⁺) 364.1012, found 364.1004.

Example 35

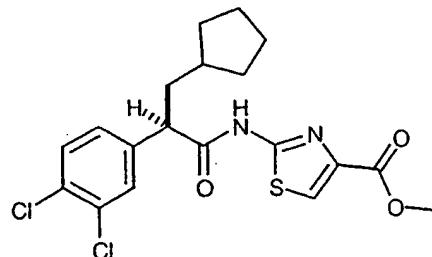
10 **3-Cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-methanesulfonyl-phenyl)-propionamide**



A solution of 2-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 3(B)(b), 130 mg, 0.29 mmol) in 15 diethyl ether (2 mL) was cooled to 0°C and then slowly treated with lithium aluminum hydride (17 mg, 0.44 mmol). The reaction mixture was allowed to warm to 25°C where it was stirred for 4 h. After 4 h at 25°C, thin layer chromatography indicated the presence of starting material. An additional amount of lithium aluminum hydride (11 mg, 0.29 mmol) was added to the reaction mixture, and the reaction mixture was allowed to stir at 20 25°C for 15 h. The reaction mixture was then slowly quenched by the dropwise addition of water. The resulting mixture was partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, ethyl acetate) afforded 3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-methanesulfonyl-phenyl)-

Example 37

(2R)-2-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester



5 A solution triphenylphosphine (164 mg, 0.63 mmol) in methylene chloride (3 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (112 mg, 0.63 mmol) in small portions. The resulting orange reaction mixture was stirred at 0°C for 20 min and then treated with (2R)-3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionic acid (prepared in Example 54, 150 mg, 0.52 mmol). The reaction mixture was stirred at 0°C for an additional 15 min and then allowed to warm to 25°C. The reaction mixture was then treated with 2-aminothiazole-4-carboxylic acid methyl ester (181 mg, 1.15 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) to afford impure (2R)-2-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester. The impure product was diluted with ethyl acetate and then washed with a saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to provide pure (2R)-2-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester (92 mg, 41%) as a white solid: mp 143-144°C;

10 20 $[\alpha]^{23}_{589} = -10.2^\circ$ (c=0.98, chloroform); EI-HRMS m/e calcd for C₁₉H₂₀Cl₂N₂O₃S (M⁺) 426.0572, found 426.0562.

stirred at -78°C for 1 h. The reaction mixture was then allowed to warm to 25°C, where it was stirred for 14 h. The reaction mixture was then acidified to pH = 2 by the dropwise addition of a 1N aqueous hydrochloric acid solution and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, chloroform then 99/1 chloroform/methanol) afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (10.28 g, 81%) as a white solid: mp 74.5-76.9°C; EI-HRMS m/e calcd for C₁₄H₁₆Cl₂O₂ (M⁺) 286.0527, found 286.0534.

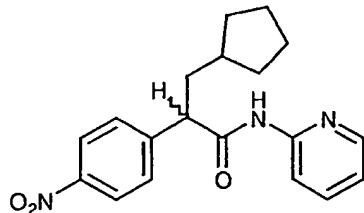
10 A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (114 mg, 0.39 mmol) in methylene chloride (10 mL) was treated with 1 drop of *N,N*-dimethylformamide and then cooled to 0°C. The reaction mixture was then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.22 mL, 0.44 mmol). The reaction mixture was stirred at 0°C for 30 min and then treated with a solution of 2-aminopyridine (78 mg, 0.83 mmol) and *N,N*-diisopropylethylamine (0.16 mL, 0.95 mmol) in tetrahydrofuran (2 mL). The resulting reaction mixture was stirred at 25°C for 14 h. The reaction mixture was then diluted with water (10 mL) and extracted with methylene chloride (2 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, hexanes then 19/1 to 15
20 4/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide (58 mg, 50%) as a white foam: EI-HRMS m/e calcd for C₁₉H₂₀Cl₂N₂O (M⁺) 362.0953, found 362.0955.

(B) In an analogous manner, there were obtained:

25 (a) From 2-amino-5-nitropyridine and 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid: 3-Cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-nitropyridin)-2-yl-propionamide as a yellow-orange foam: EI-HRMS m/e calcd for C₁₉H₁₉Cl₂N₃O₃ (M⁺) 407.0803, found 407.0799.

Example 39

(A) 3-Cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide



A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid (prepared in Example 22,
 5 263 mg, 1.0 mmol) in methylene chloride (5 mL) was cooled to 0°C and then treated with
 a 2.0M solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few
 drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min
 and then at 25°C for 1 h. The reaction mixture was then treated with a solution of 2-
 aminopyridine (207 mg, 2.2 mmol) in tetrahydrofuran (5 mL) and *N,N*-
 10 diisopropylethylamine (0.42 mL, 2.5 mmol). The reaction mixture was stirred at 25°C for
 24 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography
 (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-
 2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide (110.2 mg, 32.5%) as a white solid: mp
 152-154°C; EI-HRMS m/e calcd for C₁₉H₂₁N₃O₃ (M⁺) 339.1582, found 339.1581.

15

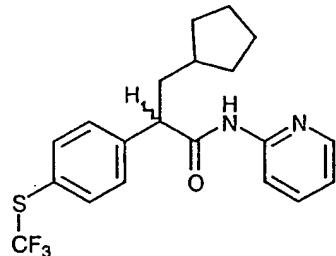
(B) In an analogous manner, there were obtained:

- (a) From 4-aminopyrimidine and 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid: 3-Cyclopentyl-2-(4-nitro-phenyl)-N-pyrimidin-4-yl-propionamide as a white solid: mp 152-153°C; EI-HRMS m/e calcd for C₁₈H₂₀N₄O₃ (M⁺) 340.1535, found 340.1533.
- 20 (b) From 2-amino-thiazole-4-carboxylic acid ethyl ester and 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid: 2-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a pale yellow solid: mp 110-115°C; EI-HRMS m/e calcd for C₂₀H₂₃N₃O₅S (M⁺) 417.1358, found 417.1346.

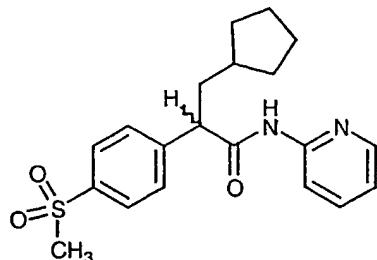
cooled to 0°C and then treated with *N*-bromosuccinimide (150 mg, 0.84 mmol) in small portions. After the complete addition of *N*-bromosuccinimide, the reaction mixture was allowed to warm to 25°C over 30 min. The orange reaction mixture was then treated with 2-aminopyridine (151 mg, 1.60 mmol), and the resulting reaction mixture was stirred at 5 25°C for 15 h. The reaction mixture was then concentrated *in vacuo* to remove methylene chloride. The remaining residue was partitioned between water and ethyl acetate. The organic layer was washed with a 1N aqueous hydrochloric acid solution, washed with a saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 10 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methylsulfanyl-phenyl)-*N*-pyridin-2-yl-propionamide (83 mg, 32%) as a white solid: mp 127-128°C; EI-HRMS m/e calcd for C₂₀H₂₄N₂OS (M⁺) 340.1609, found 340.1611.

Example 41

15 3-Cyclopentyl-*N*-pyridin-2-yl-2-(4-trifluoromethylsulfanyl-phenyl)-propionamide



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 20 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount

Example 42**3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide**

A solution of 2-aminopyridine (95 mg, 1.01 mmol) in acetonitrile (2 mL) was treated with
5 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid (prepared in Example 3(A),
250 mg, 0.84 mmol), triphenylphosphine (243 mg, 0.93 mmol), triethylamine (350 μ L,
2.53 mmol), and carbon tetrachloride (1 mL). The resulting reaction mixture was stirred
at 25°C for 15 h. The cloudy reaction mixture was diluted with water and then extracted
with methylene chloride. The organic layer was dried over magnesium sulfate, filtered,
10 and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh,
1/3 hexanes/ethyl acetate) afforded impure 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-
N-pyridin-2-yl-propionamide. Recrystallization from hexanes/methylene chloride
provided pure 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide
(170 mg, 54%) as a white solid: mp 172-173°C; EI-HRMS m/e calcd for C₂₀H₂₄N₂O₃S
15 (M⁺) 372.1508, found 372.1498.

A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.33 g, 4.18 mmol) in methanol (10 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The resulting reaction mixture was heated under reflux for 36 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol.

5 The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 97/3 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.37 g, 99%) as a light yellow oil: EI-HRMS m/e calcd for C₁₆H₁₉F₃O₂S (M⁺) 332.1058, found 332.1052.

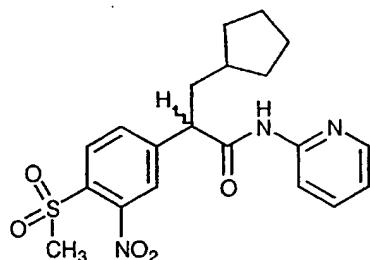
A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.14 g, 3.43 mmol) in methylene chloride (8.6 mL) was treated with 3-chloroperoxybenzoic acid (80-85% grade, 2.00 g based on 80%, 9.26 mmol). The reaction mixture was stirred at 25°C for 17 h, at which time, thin layer chromatography showed the presence of two new lower R_f products. An additional 2.00 g of 3-chloroperoxybenzoic acid was added to the reaction mixture to drive the conversion of the sulfoxide to the sulfone, and the resulting reaction mixture was stirred at 25°C for 3 d.

15 The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid methyl ester (1.19 g, 95%) as a light yellow oil: EI-HRMS m/e calcd for C₁₆H₁₉F₃O₄S (M⁺) 364.0956, found 364.0965.

(b) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and 2-amino-5-methyl pyridine: 3-Cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide as a pale yellow solid: mp 155-157°C; EI-HRMS m/e calcd for $C_{21}H_{23}F_3N_2O_3S$ (M^+) 440.1381, found 440.1376.

5 (c) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and 6-aminonicotinic acid methyl ester: 6-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester as a yellow foam: mp 58-62°C; EI-HRMS m/e calcd for $C_{22}H_{23}F_3N_2O_5S$ (M^+) 484.1280, found 484.1274.

10

Example 44**3-Cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide**

A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitrophenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS m/e calcd for $C_9H_8ClNO_4$ (M^+) 229.0142, found 229.0146.

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and

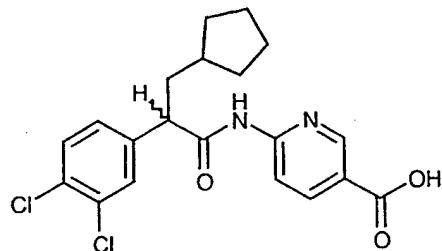
A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (865 mg, 2.43 mmol) in tetrahydrofuran (6 mL) was treated with a 0.8M aqueous lithium hydroxide solution (4.6 mL, 3.65 mmol). The reaction mixture was stirred at 5 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with water (25 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The resulting aqueous layer was then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck 10 Silica gel 60, 230-400 mesh, 1/4 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (723 mg, 87%) as a white foam. Analytical data indicated the presence of a small impurity; however, the 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid was used without further purification in subsequent reactions.

15

A solution of triphenylphosphine (138 mg, 0.53 mmol) in methylene chloride (2 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (94 mg, 0.53 mmol) in small portions. The reaction mixture was stirred at 0°C for 10 min and then treated with 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (150 mg, 0.44 mmol). 20 The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C, where it was stirred for 25 min. The reaction mixture was then treated with 2-aminopyridine (91 mg, 0.97 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide (106 mg, 58%) as a 25 white foam: mp 92-95°C (foam to gel); FAB-HRMS m/e calcd for C₂₀H₂₃N₃O₅S (M+H)⁺ 418.1436, found 418.1430.

6-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester (1.10 g, 84%) as a white foam: $[\alpha]^{23}_{D89} = -68.0^\circ$ ($c=0.128$, chloroform); FAB-HRMS m/e calcd for $C_{21}H_{22}Cl_2N_2O_3$ ($M+H$)⁺ 421.1086, found 421.1079.

5

Example 46**6-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid**

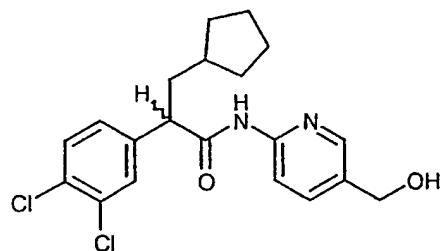
A solution of 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-carboxymethylpyridin)-2-yl-propionamide (prepared in Example 38(B)(b), 50 mg, 0.12 mmol) in ethanol (10 mL) at 10 25°C was treated with a solution of potassium hydroxide (20 mg, 0.36 mmol) in water (2 mL). The reaction was stirred at 25°C for 2 h. At this time, the reaction was diluted with water (5 mL). The ethanol was removed *in vacuo*. The aqueous layer was then acidified to pH = 2 with a 1N aqueous hydrochloric acid solution. This solution was extracted with methylene chloride (3 x 10 mL). The organic layers were dried over sodium sulfate, 15 filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate with acetic acid) afforded 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid (34 mg, 71%) as white foam: EI-HRMS m/e calcd for $C_{20}H_{20}Cl_2N_2O_3$ (M^+) 406.0851, found 406.0852.

A solution of 6-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in Example 53(B)(a), 100 mg, 0.23 mmol) in tetrahydrofuran (500 μ L) was treated with a 0.8M aqueous lithium hydroxide solution (300 μ L, 0.23 mmol). The solution was stirred at 25°C for 4 h. The reaction mixture was then directly 5 purified by column chromatography. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 methanol/ethyl acetate) afforded 6-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-nicotinic acid (65 mg, 70%) as a white solid: mp 191-193°C; FAB-HRMS m/e calcd for $C_{21}H_{24}N_2O_5S$ ($M+H$)⁺ 417.1484, found 417.1484.

10

Example 49

3-Cyclopentyl-2(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl)-propionamide



A solution of 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-carboxymethylpyridin)-2-yl-propionamide (prepared in Example 38(B)(b), 398 mg, 0.95 mmol) in diethyl ether (30 mL) cooled to 0°C was treated with lithium aluminum hydride (54 mg, 1.4 mmol). This slurry was allowed to slowly warm to 25°C. The reaction was stirred at 25°C for 16 h. At this time, the reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organics were dried over sodium sulfate, filtered, and 15 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl)-propionamide (131 mg, 35%) as a white foam: EI-HRMS m/e calcd for $C_{20}H_{22}Cl_2N_2O_2$ (M^+) 392.1058, found 392.1062.

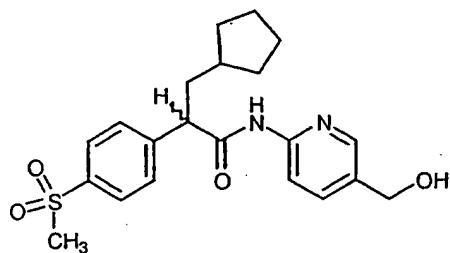
treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.35 mL, 0.7 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and then at 25°C for 30 min. The reaction mixture was then treated with 5-benzyloxy-pyridin-2-ylamine (281 mg, 1.4 mmol) and *N,N*-diisopropylethylamine (0.26 mL, 1.5 mmol). The reaction mixture was stirred at 25°C for 16 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded N-(5-benzyloxy-pyridin-2-yl)-3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide (150 mg, 50.0%) as a yellow solid: mp 47-49°C; EI-HRMS m/e calcd for C₂₆H₂₆Cl₂N₂O₂ (M⁺) 469.1449, found 469.1455.

10

A solution of N-(5-benzyloxy-pyridin-2-yl)-3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide (145.3 mg, 0.3 mmol) in methanol (5.1 mL) was treated with 10% palladium on activated carbon. The reaction mixture was stirred under hydrogen gas at 25°C for 16 h. The catalyst was then filtered off through a pad of celite (ethyl acetate). 15 The filtrate was concentrated *in vacuo* to give 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-hydroxy-pyridin-2-yl)-propionamide (92.2 mg, 78.5%) as a tan solid: mp 79-81°C; EI-HRMS m/e calcd for C₁₉H₂₀Cl₂N₂O₂ (M⁺) 378.0896, found 378.0890.

Example 52

20 **3-Cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-methanesulfonyl-phenyl)-propionamide**



A solution of 6-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in example 53(B)(a), 110 mg, 0.26 mmol) in diethyl ether

purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford impure 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-(5-methyl-pyridin-2-yl)-propionamide as a red solid. The impure product was further purified by precipitation from 1/1 hexanes/ethyl acetate to afford pure 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-(5-methyl-pyridin-2-yl)-propionamide (80 mg, 31%) as an off-white solid: mp 184-185°C; EI-HRMS m/e calcd for $C_{21}H_{26}N_2O_3S$ (M^+) 386.1664, found 386.1664.

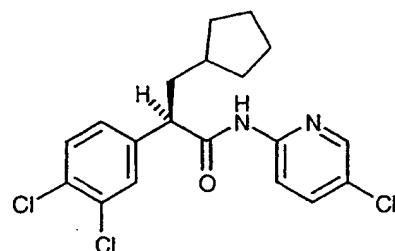
(B) In an analogous manner, there was obtained:

10 (a) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and 6-aminonicotinic acid methyl ester: 6-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester as a yellow foam: mp 82-85°C; EI-HRMS m/e calcd for $C_{22}H_{26}N_2O_5S$ (M^+) 430.1562, found 430.1571.

15

Example 54

(A) N-(5-Chloro-pyridin-2-yl)-3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide



A solution of 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionic acid (prepared in Example 38, 5.00 g, 17.4 mmol) in tetrahydrofuran (150 mL) cooled to -78°C was treated with triethylamine (2.77 mL, 19.9 mmol) followed by trimethylacetyl chloride (2.24 mL, 18.2 mmol). The resulting white slurry was stirred at -78°C for 15 min and then at 0°C for 45 min. In a separate flask, a solution of (S)-4-isopropyl-2-oxazolidinone (2.14 g, 16.57

filtered, and concentrated *in vacuo* to afforded of 3-cyclopentyl-2(R)-(3,4-dichlorophenyl)-propionic acid (928 mg, 70%) as a white solid: mp 75.1-78.3°C; $[\alpha]^{23}_{589} = -50.3^\circ$ ($c=0.100$, chloroform); EI-HRMS m/e calcd for $C_{14}H_{16}Cl_2O_2$ (M^+) 286.0527, found 286.0535.

5

A solution of triphenylphosphine (344 mg, 1.31 mmol) in methylene chloride (10 mL) cooled to 0°C was treated with *N*-bromosuccinimide (263 mg, 1.48 mmol). The reaction solution was stirred at 0°C for 5 min. At this time, 3-cyclopentyl-2-(R)-(3,4-dichlorophenyl) propionic acid (250 mg, 0.87 mmol) was added. The reaction was allowed to slowly warm to 25°C over 45 min. At this time, 5-chloro-2-aminopyridine (145 mg, 1.13 mmol) and pyridine (0.11 mL, 1.31 mmol) were added to the reaction mixture. The reaction was stirred at 25°C for 20 h. At this time, the reaction was diluted with water (10 mL) and extracted with methylene chloride (3 x 10 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded N-(5-chloro-pyridin-2-yl)3-cyclopentyl-2-(R)-(3,4-dichloro-phenyl)-propionamide (289 mg, 84%) as a white solid: mp 125-128°C; $[\alpha]^{23}_{589} = -65.6^\circ$ ($c=0.16$, chloroform); EI-HRMS m/e calcd for $C_{19}H_{19}Cl_3N_2O$ (M^+) 396.0563, found 396.0565.

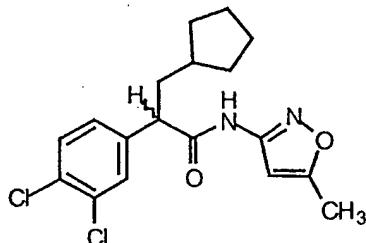
20 (B) In an analogous manner, there were obtained:

- (a) From 2-amino pyridine and 3-cyclopentyl-2-(R)-(3,4-dichloro-phenyl) propionic acid : 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide as a white foam: $[\alpha]^{23}_{589} = -56.2^\circ$ ($c=0.153$, chloroform); EI-HRMS m/e calcd for $C_{19}H_{20}Cl_2N_2O$ (M^+) 362.0953, found 362.0952.
- 25 (b) From 2-aminothiazole and 3-cyclopentyl-2-(R)-(3,4-dichloro-phenyl) propionic acid: 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-thiazol-2-yl-propionamide as a white solid: mp 133.4-136.5°C; $[\alpha]^{23}_{589} = -66.0^\circ$ ($c=0.106$, chloroform); EI-HRMS m/e calcd for $C_{17}H_{18}Cl_2N_2OS$ (M^+) 368.0517, found 368.0519.

N-(1H-imidazol-2-yl)-propionamide (81.4 mg, 33%) as a white solid: mp 58-60°C; EI-HRMS m/e calcd for C₁₇H₁₉Cl₂N₃O (M⁺) 351.0905, found 351.0901.

Example 56

5 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-isoxazol-3-yl)-propionamide



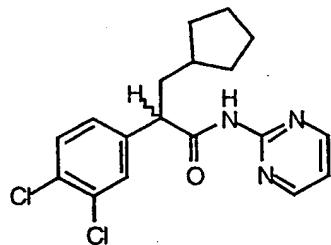
A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (prepared in Example 38, 70.7 mg, 0.25 mmol) in oxalyl chloride (215 µL, 2.46 mmol) was cooled to 0°C and then treated with 1 drop of dry *N,N*-dimethylformamide. The reaction mixture was stirred 10 at 0°C for 30 min and then stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to afford a yellow oil. This yellow oil was dissolved in a small amount of methylene chloride and then slowly added to a solution of 3-amino-5-methylisoxazole (48.3 mg, 0.49 mmol) and triethylamine (68 mL, 0.49 mmol) in methylene chloride (1.2 mL). The resulting reaction mixture was stirred at 25°C for 14 h. The reaction mixture 15 was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (100 mL) and then washed with a 10% aqueous hydrochloric acid solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-isoxazol-3-yl)- 20 propionamide (78.3 mg, 87%) as a yellow glass: mp 84-86°C; FAB-HRMS m/e calcd for C₁₈H₂₀Cl₂N₂O₂ (M+H)⁺ 367.0981, found 367.0982.

A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (prepared in Example 38, 625.2 mg, 2.18 mmol), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (908.3 mg, 2.39 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.53 mmol), and 3-aminopyridazine (310.6 mg, 3.27 mmol) in dry *N,N*-dimethylformamide (11 mL) was stirred at 25°C under nitrogen for 72 h. The reaction mixture was concentrated *in vacuo* to remove *N,N*-dimethylformamide. The resulting residue was diluted with ethyl acetate (200 mL). The organic layer was washed with a 10% aqueous hydrochloric acid solution and washed with a saturated aqueous sodium chloride solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*.

5 Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-*N*-pyridazin-3-yl-propionamide (493.8 mg, 62%) as a white foam: mp 70-71°C; EI-HRMS m/e calcd for C₁₈H₁₉Cl₂N₃O (M⁺) 363.0905, found 363.0908.

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15

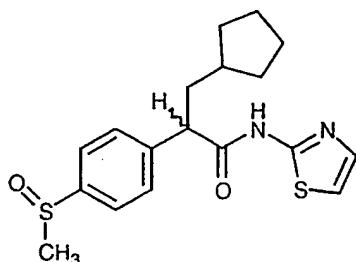
Example 59**3-Cyclopentyl-2-(3,4-dichlorophenyl)-*N*-pyrimidin-2-yl-propionamide**

A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (prepared in Example 38, 100 mg, 0.35 mmol) in methylene chloride (1 mL) was treated with 2 drops of dry 20 *N,N*-dimethylformamide. The reaction mixture was cooled to 0°C and then treated dropwise with oxalyl chloride (34 mL, 0.39 mmol). The reaction mixture was stirred at 0°C for 10 min and then stirred at 25°C for 2 h. The reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in a small amount of methylene chloride and was slowly added to a cooled (0°C) solution of 2-aminopyrimidine (67 mg, 0.70 mmol) in

phenyl)-N-pyrimidin-4-yl-propionamide (147 mg, 60%) as a white solid: mp 166.5-169.3°C; EI-HRMS m/e calcd for C₁₈H₁₉Cl₂N₃O (M⁺) 363.0905, found 363.0909.

Example 61

5 **3-Cyclopentyl-2-(4-methanesulfinyl-phenyl)-N-thiazol-2-yl-propionamide**

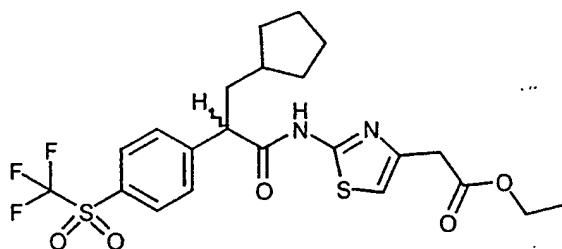


A solution of diisopropylamine (3.2 mL, 23.16 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (2.3 mL, 23.16 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(methylthio)phenylacetic acid (2.01 g, 11.03 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL). The reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (2.55 g, 12.13 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred at -78°C for 30 min and then allowed to warm to 25°C where it was stirred for 24 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 200 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methylsulfanyl-phenyl)propionic acid (1.01 g, 35%) as a cream solid: mp 91-93°C; EI-HRMS m/e calcd for C₁₅H₂₀O₂S (M⁺) 264.1184, found 264.1177.

Example 62

{2-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester

5



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfonyl-phenyl)propionic acid (1.47 g, 58%) as a cream solid: mp 69-71°C; EI-HRMS m/e calcd for C₁₅H₁₇F₃O₂S (M⁺) 318.0901, found 318.0912.

A solution of 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid methyl ester (708.2 mg, 1.94 mmol) in tetrahydrofuran (2.4 mL) was treated with a 0.8M aqueous lithium hydroxide solution (3.6 mL, 2.92 mmol). The reaction mixture was stirred at 25°C for 23 h and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous layer was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a cream solid. This solid was purified by triturating with diethyl ether/petroleum ether to provide pure 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid (527.0 mg, 77%) as a white solid: mp 143-145°C; EI-HRMS m/e calcd for C₁₅H₁₇F₃O₄S (M⁺) 350.0800, found 350.0816.

A solution of triphenylphosphine (97 mg, 0.371 mmol) in methylene chloride (1.5 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (66 mg, 0.371 mmol). The reaction mixture was stirred at 0°C for 20 min and then treated with 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid (100 mg, 0.285 mmol). The resulting reaction mixture was stirred at 0°C for 10 min, allowed to warm to 25°C, and then treated with ethyl 2-amino-4-thiazoleacetate (123 mg, 0.657 mmol). The resulting reaction mixture was stirred at 25°C for 3 d. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded {2-[3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionyl-amino]-thiazol-4-yl}-acetic acid ethyl ester (107 mg, 72%) as a yellow foam: mp 48-51°C; EI-HRMS m/e calcd for C₂₂H₂₅F₃N₂O₅S₂ (M⁺) 518.1157, found 518.1157.

A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.33 g, 4.18 mmol) in methanol (10 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The resulting reaction mixture was heated under reflux for 36 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol.

5 The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 97/3 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.37 g, 99%) as a light yellow oil: EI-HRMS m/e calcd for C₁₆H₁₉F₃O₂S (M⁺) 332.1058, found 332.1052.

10

A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.14 g, 3.43 mmol) in methylene chloride (8.6 mL) was treated with 3-chloroperoxybenzoic acid (80-85% grade, 2.00 g based on 80%, 9.26 mmol). The reaction mixture was stirred at 25°C for 17 h, at which time, thin layer chromatography showed the presence of two new lower R_f products. An additional 2.00 g of 3-chloroperoxybenzoic acid was added to the reaction mixture to drive the conversion of the sulfoxide to the sulfone, and the resulting reaction mixture was stirred at 25°C for 3 d.

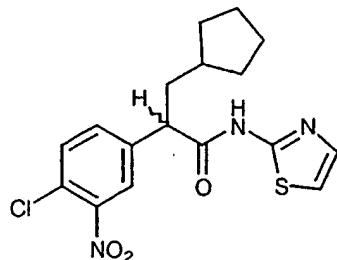
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20 The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid methyl ester (1.19 g, 95%) as a light yellow oil: EI-HRMS m/e calcd for C₁₆H₁₉F₃O₄S (M⁺) 364.0956, found 364.0965.

25

Example 64

2-(4-Chloro-3-nitro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide

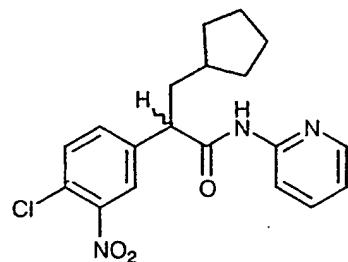


A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL)
5 was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitro-phenylacetic acid methyl ester (1.91 g,
10 89%) as a yellow oil: EI-HRMS m/e calcd for C₉H₈ClNO₄ (M⁺) 229.0142, found 229.0146.

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and
15 then treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min period. The reaction mixture turned deep purple (almost black) in color. The reaction
20 mixture was then stirred at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was then stirred at -78°C and then allowed to warm to 25°C, where it was stirred for 48 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (50 mL), and the resulting reaction

400 mesh, 3/1 hexanes/ethyl acetate). The pure 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (93 mg, 73%) was obtained as a pale yellow foam: mp 68-72°C (foam to gel); EI-HRMS m/e calcd for $C_{17}H_{18}ClN_3O_3S$ (M^+) 379.0757, found 379.0760.

5

Example 65**2-(4-Chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide**

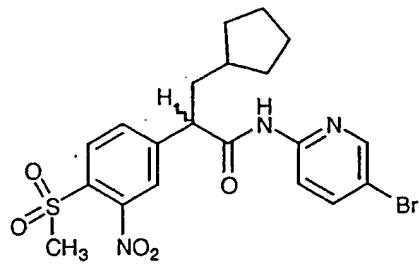
A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL)
10 was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitro-phenylacetic acid methyl ester (1.91 g,
15 89%) as a yellow oil: EI-HRMS m/e calcd for $C_9H_8ClNO_4$ (M^+) 229.0142, found 229.0146.

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and
1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and
20 then treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min

chloro-3-nitro-phenyl)-3-cyclopentyl-propionic acid (100 mg, 0.336 mmol). The resulting reaction mixture was stirred at 0°C for 10 min and then allowed to warm to 25°C, where it was stirred for 20 min. The reaction mixture was then treated with 2-aminopyridine (70 mg, 0.739 mmol). The resulting reaction mixture was stirred at 25°C
 5 for 15 h. The crude reaction mixture was treated with a solution of hexanes/ethyl acetate (2 mL, 3:1) and then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate). The pure 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide (60 mg, 48%) was obtained as a pale yellow foam: mp 48-52°C (foam to gel); EI-HRMS m/e calcd for $C_{19}H_{20}ClN_3O_3$ (M^+) 373.1193, found 373.1185.

Example 66

N-(5-Bromo-pyridin-2-yl)-3-cyclopentyl-2-(4-methanesulfonyl-3-nitro-phenyl)-propionamide



15

A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was
 20 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitrophenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS m/e calcd for $C_9H_8ClNO_4$ (M^+) 229.0142, found 229.0146.

methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (0.95 g, 84%) as a yellow gel; FAB-HRMS m/e calcd for $C_{16}H_{21}NO_6S$ ($M+H$)⁺ 356.1169, found 356.1175.

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (865 mg, 2.43 mmol) in tetrahydrofuran (6 mL) was treated with a 0.8M aqueous lithium hydroxide solution (4.6 mL, 3.65 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with water (25 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The resulting aqueous layer was then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/4 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (723 mg, 87%) as a white foam. Analytical data indicated the presence of a small impurity; however, the 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid was used without further purification in subsequent reactions.

A solution of triphenylphosphine (212 mg, 0.81 mmol) in methylene chloride (3 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (144 mg, 0.81 mmol). The reaction mixture was stirred at 0°C for 10 min and then treated with 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (250 mg, 0.73 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C, where it was stirred for 30 min. The reaction mixture was then treated with 2-amino-5-bromopyridine (279 mg, 1.61 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was directly purified by flash chromatography, (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate), to afford N-(5-bromo-pyridin-2-yl)-3-cyclopentyl-2-(4-methanesulfonyl-3-nitro-phenyl)-propionamide (121 mg, 33%) as a white foam: mp 80-83°C (foam to gel); FAB-HRMS m/e calcd for $C_{20}H_{22}BrN_3O_5S$ ($M+H$)⁺ 496.0542, found 496.0543.

warm to 25°C, where it was stirred for 48 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (50 mL), and the resulting reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue was diluted with ethyl acetate (150 mL) and water (50 mL). The organic phase was
5 washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (2.17 g, 32%) as a yellow oil: EI-HRMS m/e calcd for C₁₅H₁₈ClNO₄ (M⁺) 311.0924, found 311.0927.

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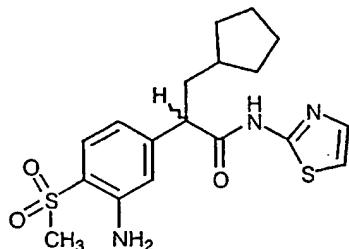
A solution of 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (1.00 g, 3.21 mmol) and sodium methanesulfinate (0.36 g, 3.53 mmol) in dimethyl sulfoxide (3 mL) was heated at 130°C for 5 h. The black reaction mixture was then poured over ice (20 g), resulting in the formation of a brown sticky substance. The resulting mixture was
15 then treated with ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (0.95 g, 84%) as a yellow
20 gel: FAB-HRMS m/e calcd for C₁₆H₂₁NO₆S (M+H)⁺ 356.1169, found 356.1175.

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (865 mg, 2.43 mmol) in tetrahydrofuran (6 mL) was treated with a 0.8M aqueous
25 lithium hydroxide solution (4.6 mL, 3.65 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with water (25 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The resulting aqueous layer was then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over

a white solid: mp 124-126°C; EI-HRMS m/e calcd for $C_{18}H_{23}N_3O_4S_2$ (M^+) 409.1130, found 409.1131.

Example 68

5 2-(3-Amino-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide



A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 10 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitrophenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS m/e calcd for $C_9H_8ClNO_4$ (M^+) 229.0142, found 229.0146.

15

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and then treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min period. The reaction mixture turned deep purple (almost black) in color. The reaction mixture was then stirred at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran was

extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/4 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (723 mg, 87%) as a white foam.

5 Analytical data indicated the presence of a small impurity; however, the 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid was used without further purification in subsequent reactions.

A solution of triphenylphosphine (138 mg, 0.53 mmol) in methylene chloride (2 mL) was
10 cooled to 0°C and then slowly treated with *N*-bromosuccinimide (94 mg, 0.53 mmol). The reaction mixture was stirred at 0°C for 10 min and then treated with 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (150 mg, 0.44 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C, where it was stirred for 25 min. The reaction mixture was then treated with 2-aminothiazole (97 mg, 0.97 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was directly purified by flash chromatography, (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate), to afford 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-thiazol-2-yl-propionamide (96 mg, 52%) as a pale yellow solid: mp 121-124°C; FAB-HRMS m/e calcd for C₁₈H₂₁N₃O₅S₂ (M+H)⁺ 424.1001, found
20 424.1000.

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-thiazol-2-yl-propionamide (100 mg, 0.236 mmol) in methanol (2 mL) was treated with a solution of ammonium chloride (27 mg, 0.500 mmol) in water (200 µL). The reaction mixture was
25 then treated with zinc dust (151 mg, 2.31 mmol). The reaction mixture was heated under reflux for 2 h. The reaction mixture was allowed to cool to 25°C and then filtered through a pad of celite. The celite pad was washed well with methanol. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 2-(3-amino-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-

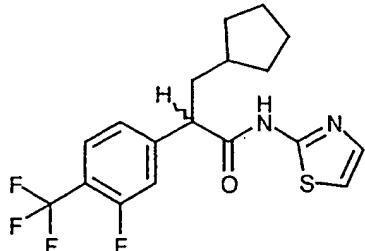
(2.50 g, 10.0 mmol) in a small amount of tetrahydrofuran. The reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (2.10 g, 10.0 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction
5 mixture was quenched with water (50 mL) and then partitioned between water (75 mL) and ethyl acetate (75 mL). The layers were shaken and separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 8/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-trifluoromethylsulfanyl-phenyl)-propionic acid methyl ester (2.95 g, 89%) as a
10 colorless oil: EI-HRMS m/e calcd for C₁₆H₁₉F₃O₂S (M⁺) 332.1058, found 332.1047.

A solution of 3-cyclopentyl-2-(3-trifluoromethylsulfanyl-phenyl)-propionic acid methyl ester (2.75 g, 8.27 mmol) in methylene chloride (30 mL) was treated with 3-chloroperoxybenzoic acid (80-85% grade, 4.28 g based on 80%, 20.67 mmol). The
15 reaction mixture was stirred at 25°C for 6 h, at which time, thin layer chromatography showed the presence of two new lower R_f products. An additional 4.00 g of 3-chloroperoxybenzoic acid was added to the reaction mixture to drive the conversion of the sulfoxide to the sulfone, and the resulting reaction mixture was stirred at 40°C for 3 d. The reaction mixture was allowed to cool to 25°C and then partitioned between water
20 (100 mL) and methylene chloride (100 mL). The layers were shaken and separated. The organic phase was washed twice with a saturated aqueous sodium bicarbonate solution, washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/methylene chloride) afforded 3-cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionic acid
25 methyl ester (2.07 g, 69%) as a colorless oil: EI-HRMS m/e calcd for C₁₆H₁₉F₃O₄S (M⁺) 364.0956, found 364.0947.

A solution of 3-cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionic acid methyl ester (1.28 g, 3.52 mmol) in tetrahydrofuran (12 mL) was treated with a 0.8M aqueous

Example 70

3-Cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide

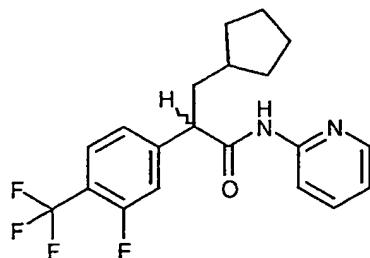


A solution of 3-fluoro-4-(trifluoromethyl)phenylacetic acid (2.50 g, 11.25 mmol) in
5 methanol (25 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The resulting reaction mixture was heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded (3-fluoro-4-trifluoromethyl-phenyl)-acetic acid methyl ester (2.58 g, 97%) as a colorless
10 oil: EI-HRMS m/e calcd for C₁₀H₈F₄O₂ (M⁺) 236.0460, found 236.0457.

A solution of diisopropylamine (1.5 mL, 10.67 mmol) in dry tetrahydrofuran (24 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (8 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (4.3 mL, 15 10.67 mmol). The resulting reaction mixture was stirred at -78°C for 45 min and then treated dropwise with a solution of (3-fluoro-4-trifluoromethyl-phenyl)-acetic acid methyl ester (2.40 g, 10.16 mmol) in a small amount of tetrahydrofuran. The reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (2.24 g, 10.67 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The 20 reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and then partitioned between water (75 mL) and ethyl acetate (75 mL). The layers were shaken and separated. The aqueous layer was further extracted with ethyl acetate (1 x 75 mL). The combined organic layers were washed with a saturated aqueous sodium

Example 71

3-Cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide

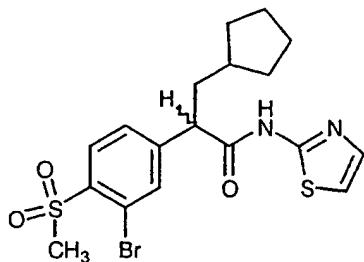


A solution of 3-fluoro-4-(trifluoromethyl)phenylacetic acid (2.50 g, 11.25 mmol) in methanol (25 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The resulting reaction mixture was heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded (3-fluoro-4-trifluoromethyl-phenyl)-acetic acid methyl ester (2.58 g, 97%) as a colorless oil: EI-HRMS m/e calcd for C₁₀H₈F₄O₂ (M⁺) 236.0460, found 236.0457.

A solution of diisopropylamine (1.5 mL, 10.67 mmol) in dry tetrahydrofuran (24 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (8 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (4.3 mL, 10.67 mmol). The resulting reaction mixture was stirred at -78°C for 45 min and then treated dropwise with a solution of (3-fluoro-4-trifluoromethyl-phenyl)-acetic acid methyl ester (2.40 g, 10.16 mmol) in a small amount of tetrahydrofuran. The reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (2.24 g, 10.67 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and then partitioned between water (75 mL) and ethyl acetate (75 mL). The layers were shaken and separated. The aqueous layer was further extracted with ethyl acetate (75 mL). The combined organic layers were washed with a saturated aqueous sodium

Example 72

2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide



5 A solution of 4-(methylthio)phenylacetic acid (21.21 g, 116.38 mmol) in methanol (291 mL) was treated slowly with concentrated sulfuric acid (3 mL). The resulting reaction mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was diluted with diethyl ether (600 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (4-methylsulfanyl-phenyl)-acetic acid methyl ester (20.95 g, 92%) as a yellow liquid which was used without further purification: EI-HRMS m/e calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{S} (\text{M}^+)$ 196.0558, found 196.0559.

15

A solution of (4-methylsulfanyl-phenyl)-acetic acid methyl ester (5.11 g, 26.03 mmol) in carbon tetrachloride (130 mL) was slowly treated with bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred at 25°C for 4 h, at which time, thin layer chromatography still indicated the presence of a substantial amount of starting material. 20 The reaction mixture was treated with more bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred an additional 4 h at 25°C and then quenched with a 10% aqueous sodium bisulfite solution (150 mL). The reaction mixture was concentrated *in vacuo* to remove carbon tetrachloride. The resulting aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate,

(300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.09 g, 94%) as a colorless oil: EI-HRMS m/e calcd for C₁₆H₁₉BrO₄S (M⁺) 388.0344, found 388.0343.

A solution of 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.62 g, 4.16 mol) in methanol (10 mL) was treated with a 1N aqueous sodium hydroxide solution (8.7 mL, 8.74 mol). The reaction mixture was stirred at 25°C for 27 h. The reaction mixture was concentrated *in vacuo* to remove methanol. The resulting aqueous residue was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 400 mL). The organic layer was washed with water (1 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.39 g, 89%) as a white solid which was used without further purification: mp 149-150°C; FAB-HRMS m/e calcd for C₁₅H₁₉BrO₄S (M+H)⁺ 375.0266, found 375.0274.

20

A solution of triphenylphosphine (168 mg, 0.64 mmol) in methylene chloride (3 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (114 mg, 0.64 mmol). The reaction mixture was stirred at 0°C for 10 min and then treated with 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (200 mg, 0.53 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 25 min. The reaction mixture was then treated with 2-aminothiazole (117 mg, 1.17 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3-bromo-4-

reaction mixture was stirred an additional 4 h at 25°C and then quenched with a 10% aqueous sodium bisulfite solution (150 mL). The reaction mixture was concentrated *in vacuo* to remove carbon tetrachloride. The resulting aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate, 5 filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 hexanes/ethyl acetate) afforded (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 85%) as a light yellow oil: EI-HRMS m/e calcd for C₁₀H₁₁BrO₂S (M⁺) 273.9663, found 273.9661.

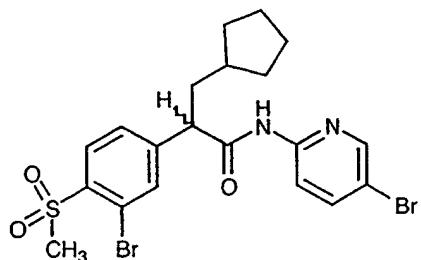
10 A solution of diisopropylamine (3.4 mL, 24.38 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (9.8 mL, 24.38 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl 15 ester (6.10 g, 22.17 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL). The resulting reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (5.59 g, 26.60 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture 20 was quenched with water (300 mL) and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl 25 acetate) afforded 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.52 g, 57%) as a light yellow oil: EI-HRMS m/e calcd for C₁₆H₂₁BrO₂S (M⁺) 356.0446, found 356.0435.

resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 25 min. The reaction mixture was then treated with 2-aminopyridine (110 mg, 1.17 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography 5 (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide (175 mg, 73%) as a white foam: mp 99-101°C; FAB-HRMS m/e calcd for $C_{20}H_{23}BrN_2O_3S$ ($M+H$)⁺ 451.0692, found 451.0689.

10

Example 74

2-(3-Bromo-4-methanesulfonyl-phenyl)-N-(5-bromo-pyridin-2-yl)-3-cyclopentyl-propionamide



A solution of 4-(methylthio)phenylacetic acid (21.21 g, 116.38 mmol) in methanol (291 15 mL) was treated slowly with concentrated sulfuric acid (3 mL). The resulting reaction mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was diluted with diethyl ether (600 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (4-methylsulfanyl-phenyl)-acetic acid methyl ester 20 (20.95 g, 92%) as a yellow liquid which was used without further purification: EI-HRMS m/e calcd for $C_{10}H_{12}O_2S$ (M^+) 196.0558, found 196.0559.

methyl ester (4.52 g, 57%) as a light yellow oil: EI-HRMS m/e calcd for $C_{16}H_{21}BrO_2S$ (M^+) 356.0446, found 356.0435.

A solution of 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.07 g, 2.99 mmol) in methylene chloride (15 mL) was treated with 3-chloroperoxybenzoic acid (57-86% grade, 1.81 g based on 57%, 5.99 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.09 g, 94%) as a colorless oil: EI-HRMS m/e calcd for $C_{16}H_{19}BrO_4S$ (M^+) 388.0344, found 388.0343.

15

A solution of 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.62 g, 4.16 mol) in methanol (10 mL) was treated with a 1N aqueous sodium hydroxide solution (8.7 mL, 8.74 mol). The reaction mixture was stirred at 25°C for 27 h. The reaction mixture was concentrated *in vacuo* to remove methanol. The resulting aqueous residue was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 400 mL). The organic layer was washed with water (1 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.39 g, 89%) as a white solid which was used without further purification: mp 149-150°C; FAB-HRMS m/e calcd for $C_{15}H_{19}BrO_4S$ ($M+H$)⁺ 375.0266, found 375.0274.

and concentrated *in vacuo* to afford (4-methylsulfanyl-phenyl)-acetic acid methyl ester (20.95 g, 92%) as a yellow liquid which was used without further purification: EI-HRMS m/e calcd for C₁₀H₁₂O₂S (M⁺) 196.0558, found 196.0559.

5 A solution of (4-methylsulfanyl-phenyl)-acetic acid methyl ester (5.11 g, 26.03 mmol) in carbon tetrachloride (130 mL) was slowly treated with bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred at 25°C for 4 h, at which time, thin layer chromatography still indicated the presence of a substantial amount of starting material. The reaction mixture was treated with more bromine (1.74 mL, 33.84 mmol). The
10 reaction mixture was stirred an additional 4 h at 25°C and then quenched with a 10% aqueous sodium bisulfite solution (150 mL). The reaction mixture was concentrated *in vacuo* to remove carbon tetrachloride. The resulting aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230
15 mesh, 9/1 hexanes/ethyl acetate) afforded (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 85%) as a light yellow oil: EI-HRMS m/e calcd for C₁₀H₁₁BrO₂S (M⁺) 273.9663, found 273.9661.

A solution of diisopropylamine (3.4 mL, 24.38 mmol) in dry tetrahydrofuran (21 mL) and
20 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (9.8 mL, 24.38 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 22.17 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-
25 tetrahydro-2(1H)-pyrimidinone (7 mL). The resulting reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (5.59 g, 26.60 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture was quenched with water (300 mL) and then concentrated *in vacuo* to remove

A solution of 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.84 g, 14.4 mol) in tetrahydrofuran (25 mL) was treated with a 0.8M aqueous lithium hydroxide solution (27 mL, 21.6 mmol). The reaction mixture was stirred at 25°C for 2.5 h. The reaction mixture was partitioned between water and ethyl acetate and
5 then acidified to pH = 2 with a 10% aqueous hydrochloric acid solution. The layers were shaken and separated. The resulting organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford crude 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (3.80 g, 82%) as a pale yellow oil that solidified to a pale yellow solid. An analytical
10 sample was obtained by recrystallization from ethyl acetate to afford 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid as a white solid: mp 180-181°C; EI-HRMS m/e calcd for C₁₆H₁₉NO₄S (M⁺) 321.1034, found 321.1039.

A solution of triphenylphosphine (98 mg, 0.37 mmol) in methylene chloride (1 mL) was
15 cooled to 0°C and then slowly treated with *N*-bromosuccinimide (67 mg, 0.37 mmol). The reaction mixture was stirred at 0°C for 15 min and then treated with 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (100 mg, 0.31 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-
20 aminothiazole (68 mg, 0.68 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (117 mg, 93%) as a white solid: mp 145-148°C; EI-HRMS m/e calcd for C₁₉H₂₁N₃O₃S₂ (M⁺) 403.1024,
25 found 403.1023.

filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 hexanes/ethyl acetate) afforded (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 85%) as a light yellow oil: EI-HRMS m/e calcd for C₁₀H₁₁BrO₂S (M⁺) 273.9663, found 273.9661.

5

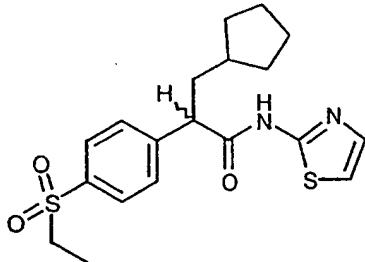
A solution of diisopropylamine (3.4 mL, 24.38 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (9.8 mL, 24.38 mmol). The reaction mixture was stirred at -78°C for 30 min and then treated 10 dropwise with a solution of (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 22.17 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL). The resulting reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (5.59 g, 26.60 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was 15 allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture was quenched with water (300 mL) and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash 20 chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.52 g, 57%) as a light yellow oil: EI-HRMS m/e calcd for C₁₆H₂₁BrO₂S (M⁺) 356.0446, found 356.0435.

25 A solution of 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.07 g, 2.99 mmol) in methylene chloride (15 mL) was treated with 3-chloroperoxybenzoic acid (57-86% grade, 1.81 g based on 57%, 5.99 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether

A solution of triphenylphosphine (98 mg, 0.37 mmol) in methylene chloride (1 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (67 mg, 0.37 mmol). The reaction mixture was stirred at 0°C for 15 min and then treated with 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (100 mg, 0.31 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminopyridine (64 mg, 0.68 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide (94.5 mg, 76%) as a yellow foam: mp 87-90°C (foam to gel); EI-HRMS m/e calcd for C₂₁H₂₃N₃O₃S (M⁺) 397.1460, found 397.1460.

Example 77

15 3-Cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide



A mixture of aluminum chloride (72.35 g, 0.54 mol) in chloroform (181 mL) was cooled to 0°C and stirred until the solid material dissolved. The reaction mixture was then slowly treated with ethyl oxalyl chloride (61 mL, 0.54 mol), and the resulting reaction mixture was stirred at 0°C for 30 min. The reaction mixture was then slowly treated with ethyl phenyl sulfide (25.00 g, 0.18 mol). The solution turned to a wine color and slowly became gum-like. The resulting reaction mixture was then stirred at 0°C for 2 h. The reaction mixture was slowly poured into a large amount of ice/water. The resulting aqueous layer was extracted with chloroform (3 x 200 mL). The combined organic layers

m/e calcd for $C_{18}H_{24}O_2S$ ($M+H$)⁺ integer mass 304, found 305. The isomeric mixture was used without further separation in subsequent reactions.

A solution of 3-cyclopentyl-2-(4-ethylsulfanyl-phenyl)-acrylic acid ethyl ester [5.76 g, 5 18.92 mmol, (E):(Z) = 1.82:1] in methylene chloride (47 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 11.45 g based on 57%, 37.83 mmol). The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-acrylic acid ethyl ester (4.89 g, 77%) as a colorless oil. The product was a 3:1 mixture of (E):(Z) isomers that was used without further purification 10 and characterization.

A solution of 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-acrylic acid ethyl ester [4.89 g, 14.53 mmol, (E):(Z) = 3:1] in ethanol (36 mL) was slowly treated with 10% palladium on activated carbon (244.5 mg). The reaction mixture was stirred under a positive pressure 20 of hydrogen gas (balloon) at 25°C and atmospheric pressure for 44 h. The catalyst was then filtered off through a pad of celite, and the celite pad was washed well with ethyl acetate. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid ethyl ester (3.50 g, 71%) as a colorless viscous oil: FAB-LRMS 25 m/e calcd for $C_{18}H_{26}O_4S$ ($M+H$)⁺ integer mass 338, found 339.

A solution of 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid ethyl ester (2.50 g, 7.39 mmol) in tetrahydrofuran (30 mL) was treated with a 0.8M aqueous lithium hydroxide solution (11.1 mL, 8.86 mmol). The reaction mixture was stirred at 25°C for

A mixture of aluminum chloride (72.35 g, 0.54 mol) in chloroform (181 mL) was cooled to 0°C and stirred until the solid material dissolved. The reaction mixture was then slowly treated with ethyl oxalyl chloride (61 mL, 0.54 mol), and the resulting reaction mixture was stirred at 0°C for 30 min. The reaction mixture was then slowly treated with 5 ethyl phenyl sulfide (25.00 g, 0.18 mol). The solution turned to a wine color and slowly became gum-like. The resulting reaction mixture was then stirred at 0°C for 2 h. The reaction mixture was slowly poured into a large amount of ice/water. The resulting aqueous layer was extracted with chloroform (3 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 hexanes/ethyl acetate) afforded 10 (4-ethylsulfanyl-phenyl)-oxo-acetic acid ethyl ester (23.64 g, 55%) as a yellow oil. The material was used without further purification and characterization in subsequent reactions.

15 A solution of iodomethylcyclopentane (4.60 g, 21.89 mmol) and triphenylphosphine (5.74 g, 21.89 mmol) in acetonitrile (22 mL) was heated under reflux for 2 weeks. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to provide an orange solid. The orange solid was triturated with diethyl ether and then filtered. The solid was washed well with diethyl ether until the washings showed the absence of 20 iodomethylcyclopentane and triphenylphosphine by thin layer chromatography. The solid was allowed to air dry to afford cyclopentylmethyl triphenylphosphonium iodide (8.92 g, 86%) as a light orange solid: mp 195-198°C; FAB-HRMS m/e calcd for C₂₄H₂₆P (M+H)⁺ 345.1772, found 345.1784.

25 A suspension of cyclopentylmethyl triphenylphosphonium iodide (24.48 g, 51.82 mmol) in dry tetrahydrofuran (100 mL) was cooled to 0°C and then treated dropwise with a 1.0M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (52 mL, 51.82 mmol). The bright orange reaction mixture was stirred at 0°C for 1 h. The reaction mixture was then treated with (4-ethylsulfanyl-phenyl)-oxo-acetic acid ethyl ester (9.50 g, 39.87 mmol).

60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid ethyl ester (3.50 g, 71%) as a colorless viscous oil: FAB-LRMS m/e calcd for $C_{18}H_{26}O_4S$ ($M+H$)⁺ integer mass 338, found 339.

- 5 A solution of 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid ethyl ester (2.50 g, 7.39 mmol) in tetrahydrofuran (30 mL) was treated with a 0.8M aqueous lithium hydroxide solution (11.1 mL, 8.86 mmol). The reaction mixture was stirred at 25°C for 23 h. The resulting reaction mixture was partitioned between water (75 mL) and ethyl acetate (75 mL) and then treated with a 1N aqueous hydrochloric acid solution (15 mL).
- 10 The layers were shaken and separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid (2.20 g, 96%) as a white solid which was used without further purification: mp 137-138°C; FAB-HRMS m/e calcd for $C_{16}H_{22}O_4S$ ($M+H$)⁺ 311.1317, found 311.1321.

15

- 15 A solution of triphenylphosphine (279 mg, 1.06 mmol) in methylene chloride (5 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (189 mg, 1.06 mmol). The reaction mixture was stirred at 0°C for 20 min and then treated with 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid (300 mg, 0.97 mmol). The resulting reaction mixture was stirred at 0°C for 10 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminopyridine (200 mg, 2.13 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide (185 mg, 50%) as a pale orange solid: mp 144-145°C; EI-HRMS m/e calcd for $C_{21}H_{26}N_2O_3S$ (M^+) 386.1664, found 386.1660.

for 3 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was slowly diluted with a saturated aqueous sodium bicarbonate solution (300 mL) and then extracted with ethyl acetate (1 x 300 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford an inseparable, isomeric mixture of (3-fluoro-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methylsulfanyl-phenyl)-acetic acid methyl ester as a yellow oil (4.65 g, 75%) which was used without further purification and characterization.

10 A solution of the inseparable, isomeric mixture of (3-fluoro-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methylsulfanyl-phenyl)-acetic acid methyl ester (4.44 g, 20.72 mmol) in methylene chloride (103 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 13.80 g based on 57%, 45.59 mmol). The reaction mixture was stirred at 25°C for 4 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 200 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 20/1 methylene chloride/ethyl acetate) afforded an inseparable, isomeric mixture of (3-fluoro-4-methanesulfonyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methanesulfonyl-phenyl)-acetic acid methyl ester as a colorless liquid (3.31 g, 65%) which was used without further purification and characterization.

25 A solution of the inseparable, isomeric mixture of (3-fluoro-4-methanesulfonyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methanesulfonyl-phenyl)-acetic acid methyl ester (2.28 g, 9.26 mmol) in dimethyl sulfoxide (23 mL) was treated with sodium thiometoxide (1.37 g, 18.52 mmol). The reaction mixture was stirred at 25°C for 4 h and then quenched with a 10% aqueous hydrochloric acid solution. The aqueous layer was extracted with chloroform (1 x 400 mL), dried over magnesium sulfate, filtered, and

The remaining residue was further diluted with water (100 mL) and then extracted with ethyl acetate (1 x 250 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.61 g, 67%) as a yellow oil: EI-HRMS m/e calcd for C₁₇H₂₄O₆S₂ (M⁺) 388.1014, found 388.1014.

A solution of 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.17 g, 3.01 mmol) in tetrahydrofuran (12 mL) was treated with a 0.8M aqueous lithium hydroxide solution (5.6 mL, 4.52 mmol). The reaction mixture was stirred at 25°C for 3 h. The resulting reaction mixture was partitioned between water (75 mL) and ethyl acetate (75 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The layers were shaken and separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.10 g, 98%) as a white foam which was used without further purification: mp 64-68°C (foam to gel); FAB-HRMS m/e calcd for C₁₆H₂₂O₆S₂ (M+H)⁺ 375.0936, found 375.0932.

A solution of triphenylphosphine (154 mg, 0.59 mmol) in methylene chloride (2 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (105 mg, 0.59 mmol). The reaction mixture was stirred at 0°C for 10 min and then treated with 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (200 mg, 0.53 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminothiazole (118 mg, 1.18 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (150 mg, 61%) as a

were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil. This yellow oil was dissolved in methanol (100 mL) and then slowly treated with concentrated sulfuric acid (5 mL). The resulting reaction mixture was heated under reflux for 3 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was slowly diluted with a saturated aqueous sodium bicarbonate solution (300 mL) and then extracted with ethyl acetate (1 x 300 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford an inseparable, isomeric mixture of (3-fluoro-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methylsulfanyl-phenyl)-acetic acid methyl ester as a yellow oil (4.65 g, 75%) which was used without further purification and characterization.

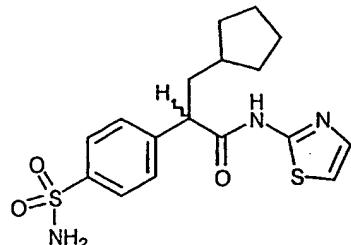
A solution of the inseparable, isomeric mixture of (3-fluoro-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methylsulfanyl-phenyl)-acetic acid methyl ester (4.44 g, 20.72 mmol) in methylene chloride (103 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 13.80 g based on 57%, 45.59 mmol). The reaction mixture was stirred at 25°C for 4 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 200 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 20/1 methylene chloride/ethyl acetate) afforded an inseparable, isomeric mixture of (3-fluoro-4-methanesulfonyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methanesulfonyl-phenyl)-acetic acid methyl ester as a colorless liquid (3.31 g, 65%) which was used without further purification and characterization.

A solution of the inseparable, isomeric mixture of (3-fluoro-4-methanesulfonyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methanesulfonyl-phenyl)-acetic acid methyl ester (2.28 g, 9.26 mmol) in dimethyl sulfoxide (23 mL) was treated with sodium

small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 64 h. The reaction mixture was quenched with water (150 mL) and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue was further diluted with water (100 mL) and then extracted with 5 ethyl acetate (1 x 250 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.61 g, 67%) as a yellow oil: EI-HRMS m/e calcd for 10 C₁₇H₂₄O₆S₂ (M⁺) 388.1014, found 388.1014.

A solution of 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.17 g, 3.01 mmol) in tetrahydrofuran (12 mL) was treated with a 0.8M aqueous lithium hydroxide solution (5.6 mL, 4.52 mmol). The reaction mixture was stirred at 15 25°C for 3 h. The resulting reaction mixture was partitioned between water (75 mL) and ethyl acetate (75 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The layers were shaken and separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.10 g, 98%) as a white foam 20 which was used without further purification: mp 64-68°C (foam to gel); FAB-HRMS m/e calcd for C₁₆H₂₂O₆S₂ (M+H)⁺ 375.0936, found 375.0932.

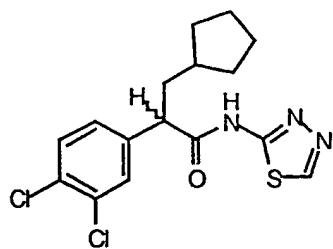
A solution of triphenylphosphine (154 mg, 0.59 mmol) in methylene chloride (2 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (105 mg, 0.59 mmol). 25 The reaction mixture was stirred at 0°C for 10 min and then treated with 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (200 mg, 0.53 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminopyridine (110 mg, 1.18 mmol). The resulting reaction mixture was stirred at 25°C

Example 82**3-Cyclopentyl-2-(4-sulfamoyl-phenyl)-N-thiazol-2-yl-propionamide**

A solution of diisopropylamine (3.3 mL, 23.5 mmol) in dry tetrahydrofuran (50 mL) and
5 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL) was cooled to -78°C under
nitrogen and then treated with a 10M solution of n-butyllithium in hexanes (2.35 mL,
23.5 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then
treated dropwise with a solution of 4-methylsulfonylphenylacetic acid (2.40 g, 11.2
mmol) in a small amount of dry tetrahydrofuran. After approximately one-half of the 4-
10 methylsulfonylphenylacetic acid in dry tetrahydrofuran was added, a precipitate formed.
Upon further addition of the remaining 4-methylsulfonylphenylacetic acid in dry
tetrahydrofuran, the reaction mixture became thick in nature. After complete addition of
the 4-methylsulfonylphenylacetic acid in dry tetrahydrofuran, the reaction mixture was
very thick and became difficult to stir. An additional amount of dry tetrahydrofuran (20
15 mL) was added to the thick reaction mixture, and the reaction mixture was stirred at -
78°C for 45 min, at which time, a solution of iodomethylcyclopentane (2.35 g, 11.2
mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction
mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture
was quenched with water (100 mL), and the resulting yellow reaction mixture was
20 concentrated *in vacuo* to remove tetrahydrofuran. The aqueous residue was acidified to
pH = 2 using concentrated hydrochloric acid. The aqueous layer was extracted with ethyl
acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated
in vacuo. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ ethyl
acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid (1.80 g,

warm to 25°C. The reaction mixture was stirred at 25°C for 30 min then heated under reflux for 20 h. The reaction mixture was cooled to 0°C and then treated with water (3 mL) followed by sodium acetate (702.5 mg, 8.56 mmol) and then finally hydroxyamine-O-sulfonic acid (484.2 mg, 4.28 mmol). The resulting reaction mixture was stirred at 0°C
5 for 30 min then allowed to warm to 25°C where it was stirred for 44 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with ethyl acetate (150 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL) and a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and
10 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/2 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-sulfamoyl-phenyl)-N-thiazol-2-yl-propionamide (191.8 mg, 72%) as a white solid: mp 179-181°C; EI-HRMS m/e calcd for C₁₇H₂₁N₃O₂S₂ (M⁺) 379.1024, found 379.1029.

15

Example 85**3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-[1,3,4]thiadiazol-2-yl-propionamide**

A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (prepared from Example 38, 200.0 mg, 0.70 mmol), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium
20 hexafluorophosphate (316.9 mg, 0.84 mmol), *N,N*-diisopropylethylamine (365 mL, 2.09 mmol), and 2-amino-1,3,4-thiadiazole (140.8 mg, 1.39 mmol) in dry *N,N*-dimethylformamide (2 mL) was stirred at 25°C under nitrogen for 20 h. The reaction mixture was concentrated *in vacuo* to remove *N,N*-dimethylformamide. The resulting residue was diluted with ethyl acetate (100 mL). The organic layer was washed with a

ester (1.60 g, 79.3%) as a clear oil: EI-HRMS m/e calcd for $C_{15}H_{19}O_2Br$ (M^+) 310.0568 found 310.0564.

A solution of 2-(4-bromo-phenyl)-3-cyclopentyl-propionic acid methyl ester (500 mg,
5 1.60 mmol) in *N,N*-dimethylformamide (4.01 mL) was treated with copper(I) cyanide
(144 mg, 1.60 mmol). The mixture was heated at 170°C for 1 h. At this time, the
reaction was cooled to 25°C and poured into aqueous ammonium hydroxide (5 mL). The
solution was diluted with water (25 mL) and extracted with ethyl acetate (3 x 35 mL).
The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash
10 chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate)
afforded 2-(4-cyano-phenyl)-3-cyclopentyl-propionic acid methyl ester (65.6 g, 15.8%) as
a clear oil: EI-HRMS m/e calcd for $C_{16}H_{19}NO_2$ (M^+) 257.1415 found 257.1406.

A solution of 2-(4-cyano-phenyl)-3-cyclopentyl-propionic acid methyl ester (65.0 mg,
15 0.25 mmol) in tetrahydrofuran/water/methanol (2.5 mL, 3:1:1) was treated with a 1N
aqueous lithium hydroxide solution (0.27 mL, 0.27 mmol). The reaction was stirred at
25°C for 6 h. At this time, the reaction was acidified to pH = 1 with a 1N aqueous
hydrochloric acid solution and extracted with chloroform/methanol (9:1, 3 x 25 mL). The
organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash
20 chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate)
afforded 2-(4-cyano-phenyl)-3-cyclopentyl-propionic acid (36.0 mg, 58.6%) as a white
solid: mp 126-128°C; EI-HRMS m/e calcd for $C_{15}H_{17}NO_2$ (M^+) 243.1259 found
243.1268.

25 A solution of 2-(4-cyano-phenyl)-3-cyclopentyl-propionic acid (33.0 mg, 0.13 mmol) in
methylene chloride (1.36 mL) was cooled to 0°C and then treated with a 2.0M solution of
oxalyl chloride in methylene chloride (0.07 mL, 0.14 mmol) and a few drops of *N,N*-
dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and at 25°C for

3.7 mmol) was then added in hexamethylphosphoramide (1 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of saturated aqueous ammonium chloride solution (10 mL). The excess solvent was removed *in vacuo*. The residue was acidified to pH = 1 with a 1N aqueous hydrochloric acid solution. The mixture was poured into water (150 mL) and extracted with ethyl acetate (3 x 100 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 95/5 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionic acid (634.9 mg, 65%) as a white solid: mp 94-95°C; FAB-HRMS m/e calcd for C₁₅H₁₇F₃O₂ (M+Na)⁺ 309.1079, found 309.1072.

A solution of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (170 mg, 0.38 mmol), 3-cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionic acid (100 mg, 0.34 mmol), and 2-aminopyridine (36 mg, 0.38 mmol) in N,N-dimethylformamide (1.75 mL) was treated with N,N-diisopropylethylamine (0.12 mL, 0.73 mmol). The reaction mixture was stirred at 25°C for 18 h. At this time, the reaction was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with a 1N aqueous hydrochloric acid solution (1 x 50 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethyl-phenyl)-propionamide (127 mg, 53.3%) as a white gum: EI-HRMS m/e calcd for C₂₀H₂₁F₃N₂O (M⁺) 362.1605, found 362.1592.

25

(B) In an analogous manner, there was obtained:

(a) From 6-amino-nicotinic acid methyl ester and 3-cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionic: 6-[3-Cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionylamino]-

The reaction mixture was stirred under hydrogen gas at 60 psi at 25°C for 18 h. The catalyst was then filtered off through a pad of celite (ethyl acetate). The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (3.52 mg, 53.3%) as a yellow oil: EI-HRMS m/e calcd for C₁₆H₂₃NO₂ (M⁺) 261.1729 found 261.1727.

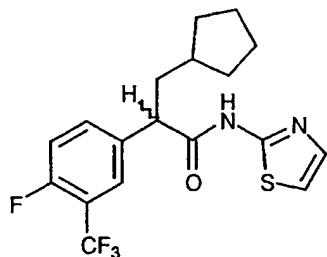
A mixture of concentrated hydrochloric acid (0.38 mL) and ice (380 mg) cooled to 0°C was treated with 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (497 mg, 1.90 mmol). After 5 min, a solution of sodium nitrite (139 mg, 2.01 mmol) in water (0.31 mL) was added to the reaction mixture. The resulting solution was stirred at 0°C for 5 min. At this time, the solution was added to a solution of n-butyl mercaptan (0.23 mL, 2.20 mmol) in water (0.41 mL) warmed to 45°C. The reaction was stirred at 45°C for 3 h. At this time, the reaction was diluted with water (50 mL) and extracted with chloroform (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude brown oil (588 mg) in methylene chloride (8.8 mL) was cooled to 0°C and treated with 3-chloroperoxybenzoic acid (80-85% grade, 1.5 g, 8.78 mmol). The reaction mixture was stirred at 25°C for 18 h. At this time, the reaction was diluted with water (75 mL) and extracted with chloroform (2 x 30 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 2-[4-(butane-1-sulfonyl)-phenyl]-3-cyclopentyl-propionic acid ethyl ester (144.3 mg, 20.7%) as a yellow oil: EI-HRMS m/e calcd for C₂₀H₃₀O₄S (M⁺) 366.1865 found 366.1858.

25

A solution of 2-[4-(butane-1-sulfonyl)-phenyl]-3-cyclopentyl-propionic acid ethyl ester (140 mg, 0.38 mmol in tetrahydrofuran/water/methanol (0.95 mL, 3:1:1) was treated with a 1N aqueous lithium hydroxide solution (0.76 mL, 0.76 mmol). The reaction was stirred at 25°C for 8 h. At this time, the reaction was acidified to pH = 1 with a 1N aqueous

Example 89

(A) 3-Cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide

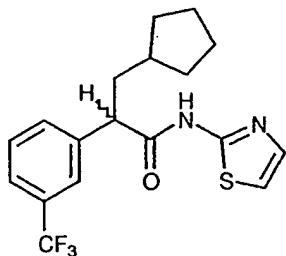


5 A solution of freshly prepared lithium diisopropylamide (35.32 mL of a 0.31M stock solution, 10.95 mmol) cooled to -78°C was treated with (4-fluoro-3-trifluoromethyl-phenyl)-acetic acid (1.11 g, 5.0 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (12.42 mL, 3:1). The resulting solution was stirred at -78°C for 1 h. Iodomethylcyclopentane (1.16 g, 5.52 mmol) was then added in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.2 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 24 h. This solution was then quenched by the slow addition of the reaction mixture to a 2N aqueous hydrochloric acid solution (50 mL). The product was extracted into ethyl acetate (1 x 300 mL) and diethyl ether (1 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (1.28 g, 84.3%) as a white solid: mp 65-68°C; EI-HRMS m/e calcd for C₁₅H₁₆F₄O₂ (M⁺) 305.1165, found 305.1174.

10 15 20 A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (304 mg, 1.0 mmol) in methylene chloride (10 mL) was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min and at 25°C for 24 h. The reaction mixture was then treated with 2-amino-thiazole (175

Example 90

3-Cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide



A solution of freshly prepared lithium diisopropylamide (35.32 mL of a 0.31M stock
 5 solution, 10.9 mmol) cooled to -78°C was treated with (3-trifluoromethyl-phenyl)-acetic acid (1.02 g, 5.0 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (12.4 mL, 3:1). The resulting solution was stirred at -78°C for 3 h. Iodomethylcyclopentane (1.16 g, 5.52 mmol) was then added in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.16 mL). The reaction mixture was stirred at -78°C for
 10 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 48 h. This solution was then quenched by the slow addition of the reaction mixture to a 2N aqueous hydrochloric acid solution (50 mL). The product was extracted into ethyl acetate (3 x 100 mL) and diethyl ether (1 x 50 mL). The organics were washed with a saturated aqueous lithium chloride solution (2 x 100 mL) and a saturated aqueous sodium chloride solution
 15 (1 x 150 mL), dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(3-trifluoromethyl-phenyl)-propionic acid (1.16 g, 80.5%) as an off-white solid: mp 64-65°C; EI-HRMS m/e calcd for C₁₅H₁₇F₃O₂ (M + Na⁺) 309.1079, found 309.1084.

20

A solution of 3-cyclopentyl-2-(3-trifluoromethyl-phenyl)-propionic acid (286 mg, 1.0 mmol) in methylene chloride (10 mL) was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few drops of N,N-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min and at 25°C

vacuo. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (1.28 g, 84.3%) as a white solid: mp 66-68°C; EI-HRMS m/e calcd for C₁₅H₁₆F₄O₂ (M⁺) 305.1165, found 305.1174.

5

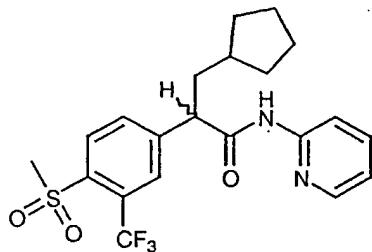
A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (7.77 g, 25.3 mmol) in methanol (50 mL) was treated slowly with concentrated sulfuric acid (0.01 mL). The resulting reaction mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (75 mL) and washed with a saturated aqueous sodium bicarbonate solution (1 x 50 mL), water (1 x 50 mL), and a saturated aqueous sodium chloride solution (4 x 50 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid methyl ester (8.48 g, 87.5%) as yellow oil: EI-HRMS m/e calcd for C₁₆H₁₈F₄O₂ (M⁺) 318.1243, found 318.1240.

A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid methyl ester (7.0 g, 21.9 mmol) in N,N-dimethylformamide (50 mL) was treated with sodium methanethiolate (2.61 g, 33.0 mmol). The reaction mixture was then heated at 100-110°C for 24 h. At this time, the reaction was poured onto a mixture of ice and a 2N aqueous hydrochloric acid solution (100 mL). This mixture was extracted into ethyl acetate (3 x 75 mL) and diethyl ether (1 x 50 mL). The organics were then washed with water (1 x 75 mL) and a saturated aqueous sodium chloride solution (3 x 100 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 85/15 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-propionic acid methyl ester (2.48g, 35.5%) as a pale yellow oil: EI-HRMS m/e calcd for C₁₇H₂₁F₃O₂S (M⁺) 346.1214 , found 346.1212.

(b) From 2-amino-thiazole-4-carboxylic acid methyl ester and 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid: 2-[3-Cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester as a white solid: mp 117-121°C; FAB-HRMS m/e calcd for C₂₁H₂₃F₃N₂O₅S₂ 5 (M+H)⁺ 504.1000, found 504.1000.

Example 92

3-Cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide



10

A solution of freshly prepared lithium diisopropylamide (141.28 mL of a 0.31M stock solution, 43.8 mmol) cooled to -78°C was treated with (4-fluoro-3-trifluoromethyl-phenyl)-acetic acid (4.44 g, 20.0 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (49.68 mL, 3:1). The resulting solution was stirred at -78°C for 1 h. At this time, the reaction was treated with a solution of iodomethylcyclopentane (4.64 g, 22.09 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (4.6 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 48 h. This solution was then quenched by the slow addition of the reaction mixture to a 2N aqueous hydrochloric acid solution. The product was extracted into ethyl acetate (3 x 400 mL) and diethyl ether (1 x 200 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-fluoro-3-

chloroperoxybenzoic acid (80-85% grade, 4.8 g, 19.8 mmol). The reaction mixture was stirred at 25°C for 4 d. At this time, the reaction was diluted with methylene chloride (25 mL). This solution was washed with a saturated aqueous sodium bisulfite solution (1 x 50 mL), water (1 x 50 mL), a saturated aqueous sodium bicarbonate solution (1 x 50 mL),
5 water (1 x 50 mL), and a saturated aqueous sodium chloride solution (3 x 50mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid ethyl ester (1.28 g, 89.0%) as a clear oil:
10 EI-HRMS m/e calcd for C₁₈H₂₃F₃O₄S (M⁺) 392.1269 found 392.1268.

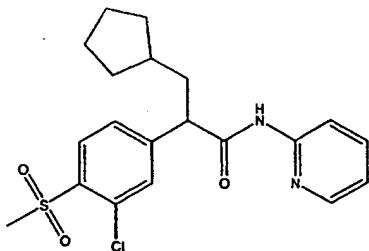
A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid ethyl ester (707mg, 1.80 mmol in tetrahydrofuran/water (24 mL, 3:1) was treated with lithium hydroxide (166 mg, 3.97 mmol). The reaction was stirred at 25°C for 24 h.
15 At this time, the reaction concentrated *in vacuo*. The residue was diluted with water (25 mL) and extracted with diethyl ether (1 x 15 mL). The aqueous layer was acidified to pH = 1 with a 2N aqueous hydrochloric acid solution, and extracted with chloroform (3 x 25 mL). The organics were washed with water (1 x 25 mL), a saturated aqueous sodium chloride solution (3 x 25 mL), dried over magnesium sulfate, filtered, and concentrated *in*
20 *vacuo* to afford 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid (426.7 mg, 65%) as a white solid: mp 122-123°C; EI-HRMS m/e calcd for C₁₆H₁₉F₃O₄S (M⁺) 364.0956 found 364.0956.

A solution of and 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-
25 propionic acid (73 mg, 0.2 mmol) and triphenylphosphine (79 mg, 0.3 mmol) in methylene chloride (5.0 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (60.5 mg, 0.34 mmol). After the complete addition of *N*-bromosuccinimide, the reaction mixture was allowed to warm to 25°C over 30 min. The reaction mixture was then treated with 2-aminopyridine (28.2 mg, 0.3mmol) and pyridine

A solution of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (188 mg, 0.42 mmol) and 3-cyclopentyl-2-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-propionic acid (94 mg, 0.28 mmol) in *N,N*-dimethylformamide (5 mL) was treated with *N,N*-diisopropylethylamine (150 μ L, 0.85 mmol) and 2-aminothiazole (42.5 mg, 0.42 mmol). The mixture was stirred at 25°C for 48 h. At this time, the reaction mixture was poured into cold water (25 mL) containing a 1N aqueous hydrochloric acid solution (50 mL) and extracted into ethyl acetate (2 x 75 mL) and diethyl ether (1 x 25 mL). The organics were then washed with water (2 x 75 mL) and a saturated aqueous sodium chloride solution (3 x 75 mL), dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide (50.5 mg, 43.1%) as a clear oil: FAB-HRMS m/e calcd for $C_{19}H_{21}F_3N_2OS_2$ ($M+H$)⁺ 415.1125, found 415.1123.

Example 94

2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide



A solution of aluminum trichloride (34.8 g, 261.4 mmol) in chloroform (120 mL) under argon and cooled to 0°C and was then treated dropwise with a solution of ethyl chlorooxacetate (18.7 mL, 167.5 mmol) in chloroform (120 mL). The mixture was then stirred at 0°C for 30 min. After this time a solution of 2-chlorothioanisole (25.0 g, 156.5 mmol) in chloroform (120 mL) was added dropwise to the above mixture at 0°C and it

acrylic acid ethyl ester (95 mg, 86%, mixture of E and Z isomers (2:1)) as a colorless oil and taken on without characterization.

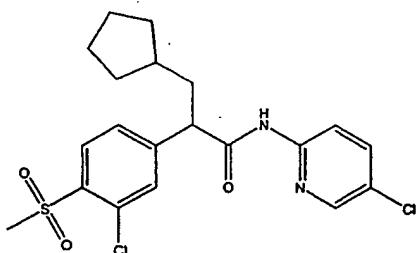
The mixture of E and Z isomers of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-
5 acrylic acid ethyl ester (1.04 g, 2.91 mmol), nickel chloride hexahydrate (69 mg, 0.29
mmol) and methanol (25 mL) were placed in a flask under argon. To this green solution
was then added sodium borohydride (221 mg, 5.83 mmol) slowly in small portions using
an ice bath if necessary to keep the temperature at 20°C. The solution turned black and a
fine precipitate formed after addition of the sodium borohydride. This was then stirred at
10 25°C for 1.5 h. After such time the reaction was filtered through celite and washed with
methanol. The filtrate and washings were combined and concentrated *in vacuo* to reduce
the volume. The residual solution was then diluted with water (15 mL) and extracted
with ethyl acetate (3 x 15 mL) dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl
15 acetate) afforded a mixture of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-
propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-
propionic acid ethyl ester (transesterification occurred under the reaction conditions) (937
mg) as a clear colorless oil. (It was carried on without characterization because it was a
mixture of esters)

20

The mixture of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid
methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid
ethyl ester, from above, (937 mg) was dissolved in ethanol (30 mL) and allowed to
dissolve. To this solution was then added a solution of potassium hydroxide (733 mg,
25 13.1 mmol) in water (7 mL). The yellow solution was then stirred for 3 h at 25°C. It was
concentrated *in vacuo* to remove the ethanol and then 1N hydrochloric acid was added
until the pH = 2. This was then extracted with methylene chloride (3 X 15 mL). The
organic layers were then dried over sodium sulfate, filtered and concentrated *in vacuo*.
Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate

reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 94, 200 mg, 0.61 mmol) and stirred at 0°C for 20 min and then warmed to 25°C where it was stirred 5 for 30 min. After such time, the reaction mixture was treated with 2-amino-5-bromopyridine (157 mg, 0.91 mmol) and pyridine (0.088 mL, 1.09 mmol), and reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash 10 chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-(5-bromo-pyridin-2-yl)-propionamide (245 mg, 83%) as a white foam: EI-HRMS m/e calcd for C₂₀H₂₂BrClN₂O₃S (M⁺) 484.0223, found 484.0222.

15

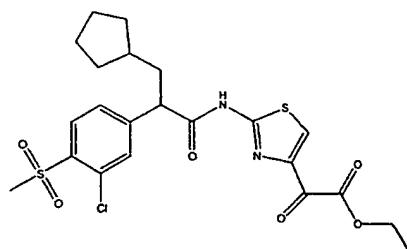
Example 96**N-(5-Chloro-pyridin-2-yl)-2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide**

A solution of triphenylphosphine (238 mg, 0.91 mmol) in methylene chloride (10 mL) 20 was cooled to 0°C and then treated with *N*-bromosuccinimide (183 mg, 1.03 mmol). The reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 94, 200 mg, 0.61 mmol) and stirred at 0°C for 20 min and then warmed to 25°C where it was stirred

organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 60/40 hexanes/ethyl acetate) afforded 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide (122 mg, 43%) as a white foam: EI-HRMS m/e calcd for 5 $C_{20}H_{22}ClF_3N_2O_3S (M^+)$ 474.0992, found 474.0990.

Example 98

{2-[2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-oxo-acetic acid ethyl ester



10

A solution of triphenylphosphine (238 mg, 0.91 mmol) in methylene chloride (10 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (183 mg, 1.03 mmol). The reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 94, 200 mg, 0.61 mmol) and stirred at 0°C for 20 min and then warmed to 25°C where it was stirred for 30 min. After such time, the reaction mixture was treated with 2-(amino-thiazol-4-yl)-oxo-acetic acid ethyl ester (182 mg, 0.91 mmol) and pyridine (0.088 mL, 1.09 mmol), and the reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with 15 water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 20 {2-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionylamino]-

25%) as a white foam: $[\alpha]^{23}_{589} = -93.9^\circ$ (c=0.165, chloroform); FAB-HRMS m/e calcd for $C_{25}H_{28}ClNO_5S$ ($M+H$)⁺ 490.1455, found 490.1443.

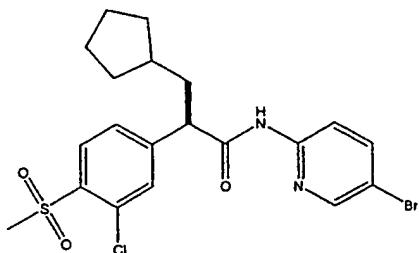
A solution of lithium hydroxide (215 mg, 9.0 mmol) in water (2.8 mL) was treated with a
5 30% aqueous hydrogen peroxide solution (2.0 mL, 18 mmol). This freshly prepared lithium hydroperoxide solution was then cooled to 0°C and then slowly added to a cooled (0°C) solution of 4(R)-benzyl-3-[2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-oxazolidin-2-one (2.20 g, 4.5 mmol) in tetrahydrofuran (18 mL) and water (5.8 mL). After 1.5 h at 0°C, the reaction was quenched with a 1.5N aqueous
10 sodium sulfite solution (25 mL) and was diluted with water (150 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL). The aqueous layer was then acidified with a 1N aqueous hydrochloric acid solution to pH = 2 and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25
15 hexanes/ethyl acetate with 1% acetic acid) afforded 2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.26 g, 85%) as a white solid: mp 106.1-108.8°C; $[\alpha]^{23}_{589} = -43.0^\circ$ (c=0.172, chloroform); EI-HRMS m/e calcd for $C_{15}H_{19}ClO_4S$ (M^+) 330.0692, found 330.0690.

20 A solution of triphenylphosphine (248 mg, 0.94 mmol) in methylene chloride (9 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (190 mg, 1.07 mmol). The reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (208 mg, 0.63 mmol). The
25 reaction mixture was stirred at 0°C for 20 min and then warmed to 25°C where it was stirred for 30 min. After such time, the reaction mixture was treated with 2-aminothiazole (95 mg, 0.94 mmol) and pyridine (0.092 mL, 1.13 mmol), and the reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic layers

81.5%) as a white foam: $[\alpha]^{23}_{589} = -41.8^\circ$ ($c=0.098$, chloroform); EI-HRMS m/e calcd for $C_{20}H_{23}ClN_2O_3S (M^+)$ 406.1118, found 406.1119.

Example 101

5 N-(5-Bromo-pyridin-2-yl)-2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide

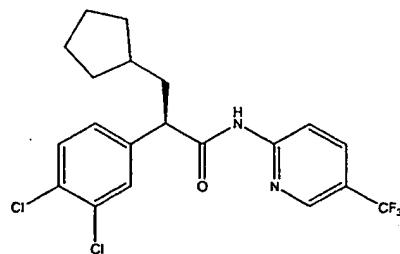


A solution of triphenylphosphine (238 mg, 0.91 mmol) in methylene chloride (10 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (183 mg, 1.03 mmol). The reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 99, 200 mg, 0.61 mmol). The reaction mixture was stirred at 0°C for 20 min and then warmed to 25°C where it was stirred for 30 min. After such time, the reaction mixture was treated with 2-aminopyridine (85 mg, 0.91 mmol) and pyridine (0.088 mL, 1.09 mmol), and the reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Biotage chromatography (FLASH 40S, Silica, 60/40 hexanes/ethyl acetate) afforded N-(5-bromo-pyridin-2-yl)-2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide (222 mg, 76%) as an off-white foam: $[\alpha]^{23}_{589} = -48.6^\circ$ ($c=0.105$, chloroform); EI-HRMS m/e calcd for $C_{20}H_{22}BrClN_2O_3S (M^+)$ 484.0223, found 484.0223.

were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 85/15 hexanes/ethyl acetate) afforded N-(5-cyano-pyridin-2-yl)-3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide (882 mg, 73%) as a pink foam: EI-HRMS m/e calcd for C₂₀H₁₉Cl₂N₃O (M⁺) 387.0905, 5 found 387.0905.

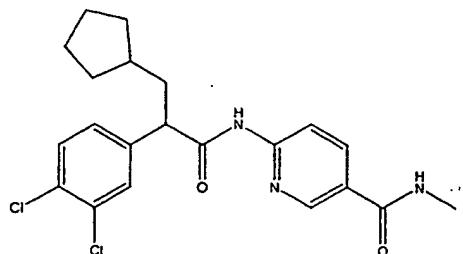
Example 103

3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

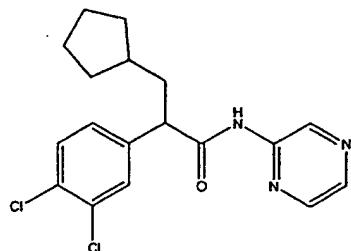


10

A solution of 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionic acid (prepared in Example 54, 200 mg, 0.69 mmol) in methylene chloride (10 mL) and one drop of *N,N*-dimethylformamide was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.42 mL, 0.84 mmol). Gas evolution began immediately. 15 The reaction mixture was allowed to warm slowly to 25°C where it was stirred for 30 min. After this time, the reaction mixture was treated with a solution of *N,N*-diisopropylethylamine (0.24 mL, 1.39 mmol) and 5-trifluoromethyl-2-aminopyridine (150 mg, 0.905 mmol) in tetrahydrofuran (4 mL) in one portion. The resulting reaction mixture was stirred for 16 h at 25°C. After such time, the reaction was diluted with water 20 (15 mL) and was extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded the 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-trifluoromethyl-pyridin-2-yl)-

Example 105**6-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-N-methyl-nicotinamide**

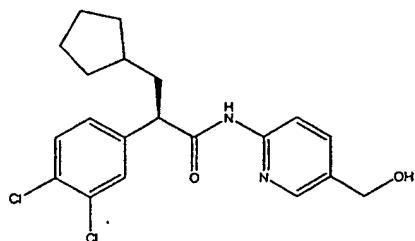
A solution of 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid (prepared in Example 46, 125 mg, 0.31 mmol), *N,N*-diisopropylethylamine (0.10 mL, 0.61 mmol), and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (142 mg, 0.32 mmol) in *N,N*-dimethylformamide (15 mL) at 25°C was treated dropwise with a 2.0M solution of methylamine in tetrahydrofuran (0.16 mL, 0.32 mmol). The resulting reaction mixture was stirred at 25°C for 16 h. The reaction mixture was then diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-N-methyl-nicotinamide (83 mg, 64%) as white solid: mp 229.1-231.7°C; FAB-HRMS m/e calcd for C₂₁H₂₃Cl₂N₃O₂ (M+H)⁺ 420.1245, found 420.1247.

Example 106**3-Cyclopentyl-2-(3,4-dichloro-phenyl)-N-pyrazin-2-yl-propionamide**

stirred for 30 min. After such time, the reaction mixture was treated with 2-amino-5-bromopyridine (271 mg, 1.57 mmol) and pyridine (0.15 mL, 1.88 mmol). The resulting reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with water (10 mL) and extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded N-(5-bromo-pyridin-2-yl)-3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide (448 mg, 97%) as a white solid: mp 107.3-109.9°C; $[\alpha]^{23}_{589} = -66.7^\circ$ (c=0.084, chloroform); EI-HRMS m/e calcd for C₁₉H₁₉BrCl₂N₂O (M⁺) 440.0058, found 10 440.0056.

Example 108

3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl) propionamide



15

A solution of 6-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in Example 45, 398 mg, 0.95 mmol) in diethyl ether (30 mL) was cooled to 0°C and then treated with lithium aluminum hydride (54 mg, 1.4 mmol) in one portion. There was immediate gas evolution. The reaction mixture was allowed to 20 slowly warm to 25°C and was stirred at 25°C 16 h. After such time, the reaction mixture was diluted with water (10 mL) and then extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-

the iodine solution, the cooling bath was removed, and the reaction mixture was allowed to warm to 25°C where it was stirred for 2 h. The reaction mixture was then poured into a solution consisting of a saturated aqueous ammonium chloride solution (400 mL) and ammonium hydroxide (100 mL), and the organic compound was extracted into ethyl acetate (3 x 200 mL). The combined organic extracts were successively washed with a saturated aqueous sodium thiosulfate solution (1 x 400 mL) and a saturated aqueous sodium chloride solution (1 x 400 mL). The organic layer was then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 20/1 to 10/1 hexanes/diethyl ether) afforded (E)-3-
5 cycloheptyl-2-iodo-acrylic acid methyl ester (17.86 g, 64%) as a colorless oil: EI-HRMS
10 m/e calcd for C₁₁H₁₇IO₂ (M⁺) 308.0273, found 308.0273.

A mixture of zinc dust (2.6 g, 40 mmol, Aldrich, -325 mesh) and dry tetrahydrofuran (3 mL) under argon was treated with 1,2-dibromoethane (0.38 g, 2 mmol). The zinc
15 suspension was then heated with a heat gun to ebullition, allowed to cool, and heated again. This process was repeated three times to make sure the zinc dust was activated. The activated zinc dust suspension was then treated with trimethylsilyl chloride (220 mg, 2 mmol), and the suspension was stirred for 15 min at 25°C. The reaction mixture was then treated dropwise with a solution of (E)-3-cycloheptyl-2-iodo-acrylic acid methyl
20 ester (6.16 g, 20 mmol) in dry tetrahydrofuran (5 mL) over 10 min. The reaction mixture was then stirred at 40-45°C for 1 h and then stirred overnight at 25°C. The reaction mixture was then diluted with dry tetrahydrofuran (10 mL), and the stirring was stopped to allow the excess zinc dust to settle down (~2 h). In a separate reaction flask,
bis(dibenzylideneacetone)palladium(0) (270 mg, 0.5 mmol) and triphenylphosphine (520
25 mg, 2 mmol) in dry tetrahydrofuran (25 mL) was stirred at 25°C under argon for 10 min and then treated with 4-bromophenyl methyl sulfone (4.23 g, 18 mmol) and the freshly prepared zinc compound in tetrahydrofuran. The resulting brick red solution was heated at 50°C for 24 h. The reaction mixture was cooled to 25°C and then poured into a saturated aqueous ammonium chloride solution (150 mL), and the organic compound was
30 extracted into ethyl acetate (3 x 150 mL). The combined organic extracts were washed

chloride solution (1 x 50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford 3-cycloheptyl-2-(4-methanesulfonyl-phenyl)-propionic acid (78 mg, 86%) as a white solid: EI-HRMS m/e calcd for C₁₇H₂₄O₄S (M+H)⁺ 325.1474, found 325.1478.

5

A solution of triphenylphosphine (116 mg, 0.44 mmol) in methylene chloride (2 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (78 mg, 0.44 mmol). The reaction mixture was stirred at 0°C for 30 min and then treated with a solution of 3-cycloheptyl-2-(4-methanesulfonyl-phenyl)-propionic acid (72 mg, 0.22 mmol) in 10 methylene chloride (2 mL). The clear solution was stirred for 10 min at 0°C and then allowed to warm to 25°C where it was stirred for 1.5 h. The reaction mixture was then treated with 2-aminothiazole (66 mg, 0.66 mmol), and the resulting suspension was stirred for 20 h at 25°C. The reaction mixture was then concentrated *in vacuo* to remove 15 methylene chloride, and the residue was diluted with ethyl acetate (30 mL) and a 1N aqueous hydrochloric acid solution (30 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (1 x 10 mL). The combined organic extracts were successively washed with a saturated aqueous sodium bicarbonate solution (1 x 20 mL) and a saturated aqueous sodium chloride solution (1 x 30 mL), dried over 20 anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Biotage chromatography (FLASH 40S, Silica, 4/1 to 1/1 hexanes/ethyl acetate) afforded 3-cycloheptyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide (68 mg, 76%) as an amorphous solid: EI-HRMS m/e calcd for C₂₀H₂₆N₂O₃S₂ (M⁺) 406.1426, found 406.1424.

poured into a solution consisting of a saturated aqueous ammonium chloride solution (400 mL) and ammonium hydroxide (100 mL), and the organic compound was extracted into ethyl acetate (3 x 250 mL). The combined organic extracts were successively washed with a saturated aqueous sodium thiosulfate solution (1 x 500 mL) and a saturated aqueous sodium chloride solution (1 x 500 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 9/1 hexanes/diethyl ether) afforded (E)-3-cyclohexyl-2-iodo-acrylic acid methyl ester (26.3 g, 99%) as a light pink oil: EI-HRMS m/e calcd for C₁₀H₁₅IO₂ (M⁺) 294.0117, found 294.0114.

10

A mixture of zinc dust (2.6 g, 40 mmol, Aldrich, -325 mesh) and dry tetrahydrofuran (3 mL) under argon was treated with 1,2-dibromoethane (0.37 g, 2 mmol). The zinc suspension was then heated with a heat gun to ebullition, allowed to cool, and heated again. This process was repeated three times to make sure the zinc dust was activated.

15 The activated zinc dust suspension was then treated with trimethylsilyl chloride (217 mg, 2 mmol), and the suspension was stirred for 15 min at 25°C. The reaction mixture was then treated dropwise with a solution of (E)-3-cyclohexyl-2-iodo-acrylic acid methyl ester (5.88 g, 20 mmol) in dry tetrahydrofuran (5 mL) over 5 min. During the addition, the temperature rose to 50°C. The reaction mixture was then stirred at 40-45°C for 1 h and

20 then stirred overnight at 25°C. The reaction mixture was then diluted with dry tetrahydrofuran (10 mL), and the stirring was stopped to allow the excess zinc dust to settle down (~2 h). In a separate reaction flask, bis(dibenzylideneacetone)palladium(0) (270 mg, 0.5 mmol) and triphenylphosphine (520 mg, 2 mmol) in dry tetrahydrofuran (25 mL) was stirred at 25°C under argon for 10 min and then treated with 4-bromophenyl

25 methyl sulfone (4.23 g, 18 mmol) and the freshly prepared zinc compound in tetrahydrofuran. The resulting brick red solution was heated at 50°C for 24 h, at which time, thin layer chromatography analysis of the reaction mixture indicated the absence of starting material. The reaction mixture was cooled to 25°C and then poured into a saturated aqueous ammonium chloride solution (150 mL), and the organic compound was

30 extracted into ethyl acetate (3 x 100 mL). The combined organic extracts were washed

mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclohexyl-2-(4-methanesulfonyl-phenyl)-propionic acid (570 mg, 60%) as a white solid: mp 139-143°C; EI-HRMS m/e calcd for C₁₆H₂₂O₄S (M⁺) 310.1239, found 310.1241.

5

A solution of triphenylphosphine (416 mg, 1.58 mmol) in methylene chloride (8 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (281 mg, 1.58 mmol). The reaction mixture was stirred at 0°C for 30 min and then treated with a solution of 3-cyclohexyl-2-(4-methanesulfonyl-phenyl)-propionic acid (290 mg, 0.93 mmol) in 10 methylene chloride (5 mL). The clear solution was stirred for 15 min at 0°C and then allowed to warm to 25°C where it was stirred for 1.5 h. The reaction mixture was then treated with 2-aminothiazole (233 mg, 2.32 mmol), and the resulting suspension was stirred for 20 h at 25°C. The reaction mixture was concentrated *in vacuo* to remove 15 methylene chloride, and the residue was diluted with ethyl acetate (50 mL) and a 1N aqueous hydrochloric acid solution (50 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (1 x 30 mL). The combined organic extracts were successively washed with a saturated aqueous sodium bicarbonate solution (1 x 50 mL) and a saturated aqueous sodium chloride solution (1 x 50 mL), dried over 20 anhydrous magnesium sulfate, filtered, and, concentrated *in vacuo*. Biotage chromatography (FLASH 40S, Silica, 4/1 to 1/1 hexanes/ethyl acetate) afforded 3-cyclohexyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide (337 mg, 92%) as an amorphous solid: EI-HRMS m/e calcd for C₁₉H₂₄N₂O₃S₂ (M⁺) 392.1228, found 392.1230.

chromatography (Merck Silica gel 60, 230-400 mesh 80/20 hexanes/ ethyl acetate) afforded 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid methyl ester (1.63 g, 46.8%) as pale yellow oil: EI-HRMS m/e calcd for $C_{15}H_{19}NO_4 (M^+)$ 277.1314, found 277.1317.

5 A solution of 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid methyl ester (0.55 g, 2.0 mmol) in tetrahydrofuran/water (12 mL, 3:1) was treated with lithium hydroxide (185 mg, 4.40 mmol). The reaction was stirred at 25°C for 48 h. The tetrahydrofuran was then removed *in vacuo*. The residue was diluted with water (25 mL) and extracted with ether (1 x 20 mL). The aqueous layer was acidified to pH = 2 with a 3N aqueous hydrochloric acid solution. The solution was extracted with methylene chloride (3 x 25 mL). The organics were washed with a saturated aqueous sodium chloride solution (2 x 25 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid (0.48 g, 91.9%) as a tan solid: mp 95-99°C; EI-HRMS m/e calcd for $C_{14}H_{17}NO_4 (M^+)$ 263.1157, found 263.1156.

15

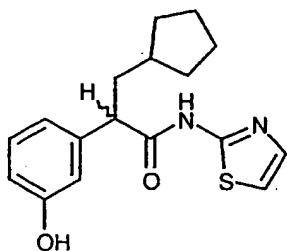
A solution of 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid (432 mg, 1.64 mmol) in methylene chloride (16 mL) was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.90 mL, 1.80 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min and at 25°C for 20 1.2 h. The reaction mixture was then treated with a solution of 2-aminothiazole (361.4 mg, 3.61 mmol) and *N,N*-diisopropylethylamine (0.70 mL, 3.93 mmol) in tetrahydrofuran (16 mL). The reaction mixture was stirred at 25°C for 6 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(nitrophenyl)-N-thiazol-2-yl-propionamide (409.3 mg, 72.2%) as a tan solid: mp 171-174°C; EI-HRMS m/e calcd for $C_{17}H_{19}N_3O_3S (M^+)$ 345.1147, found 345.1153.

of chloroform/methanol (9:1). The organics were dried over sodium sulfate, filtered, and concentrated in *vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate with glacial acetic acid) afforded 3-cyclopentyl-2-(3-methoxy-phenyl)-propionic acid (1.05 g, 79.8%) as a clear wax: EI-HRMS m/e calcd for C₁₅H₂₀O₃ 5 (M⁺) 248.1412, found 248.1409.

A solution of 3-cyclopentyl-2-(3-methoxy-phenyl)-propionic acid (500 mg, 2.0 mmol) in methylene chloride (20 mL) cooled to 0°C was treated with a 2.0M solution of oxalyl chloride in methylene chloride (1.1 mL, 2.20 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min then at 25°C for 10 min. The reaction mixture was then treated with 2-aminothiazole (444 mg, 4.42 mmol) and *N,N*-diisopropylethylamine (0.84 mL, 4.83 mmol) in tetrahydrofuran (10.1 mL). This solution was stirred at 25°C for 18 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-methoxy-phenyl)-N-thiazol-2-yl-propionamide (549mg, 82.6%) as a white solid: mp 44-45°C; EI-HRMS m/e calcd for C₁₈H₂₂N₂O₂S (M⁺) 330.1402 found 330.1398.

Example 113

20 **3-Cyclopentyl-2-(3-hydroxy-phenyl)-N-thiazol-2-yl-propionamide**



A 1.0M solution of boron tribromide in methylene chloride (3.53 mL, 3.53 mmol) at 25°C was treated with a solution of 3-cyclopentyl-2-(3-methoxy-phenyl)-N-thiazol-2-yl-propionamide (prepared in Example 112, 0.11 g, 0.35 mmol) in methylene chloride (3.5

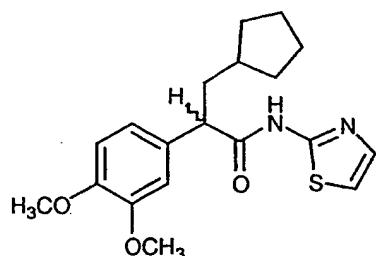
sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethoxy-phenyl)-propionic acid (0.31 g, 30.6%) as a tan solid: mp 62-64°C; EI-HRMS m/e calcd for C₁₅H₁₇F₃O₃ (M⁺) 302.1129 found 302.1131.

5

A solution of 3-cyclopentyl-2-(4-trifluoromethoxy-phenyl)-propionic acid (0.16 g, 0.52 mmol) in methylene chloride (5.3 mL) cooled to 0°C was treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.29 mL, 0.58 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and at 25°C for 10 min. The reaction mixture was then treated with a solution of 2-aminothiazole (0.11 g, 1.16 mmol) and *N,N*-diisopropylethylamine (0.22 mL, 1.27 mmol) in tetrahydrofuran (2.65 mL). The reaction mixture was stirred at 25°C for 18 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethoxy-phenyl)-propionamide (203.8 mg, 100%) as a white solid: mp 168-170°C; EI-HRMS m/e calcd for C₁₈H₁₉F₃N₂O₂S (M⁺) 384.1119, found 384.1118.

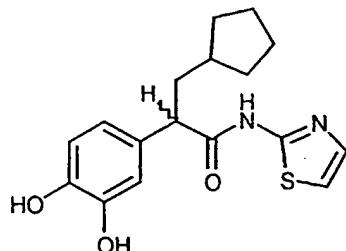
Example 115

3-Cyclopentyl-2-(3,4-dimethoxy-phenyl)-N-thiazol-2-yl-propionamide



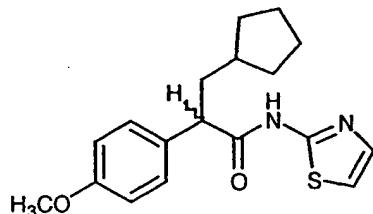
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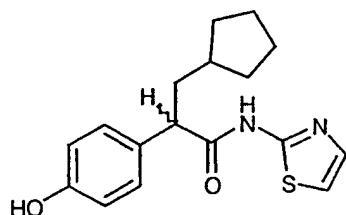
A solution of freshly prepared lithium diisopropylamide (58.5 mL of a 0.91M stock solution, 53.2 mmol) cooled to -78°C was treated with (3,4-dimethoxy-phenyl)-acetic acid (4.97 g, 25.3 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

Example 116**3-Cyclopentyl-2-(3,4-dihydroxy-phenyl)-N-thiazol-2-yl-propionamide**

A 1.0M solution of boron tribromide in methylene chloride (7.43 mL, 7.43 mmol) at 5 25°C was treated with a solution of 3-cyclopentyl-2-(3,4-dimethoxy-phenyl)-N-thiazol-2-yl-propionamide (prepared in Example 115, 0.27 g, 0.74 mmol) in methylene chloride (7.43 mL). This solution was stirred at 25°C for 1 h. At this time, the reaction was cooled to 0°C and treated with a dilute aqueous ammonium hydroxide solution. This mixture was stirred at 0°C for 20 min. At this time, the reaction was poured into water 10 and was extracted with chloroform (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dihydroxy-phenyl)-N-thiazol-2-yl-propionamide (38.8 mg, 15.7%) as a white solid: mp 170-173°C; EI-HRMS m/e calcd for C₁₇H₂₀N₂O₃S (M⁺) 332.1194 found 332.1192.

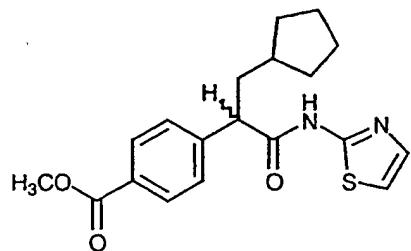
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Example 117**3-Cyclopentyl-2-(4-methoxy-phenyl)-N-thiazol-2-yl-propionamide**

Example 118**3-Cyclopentyl-2-(4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide**

5 A solution 3-cyclopentyl-2-(4-methoxy-phenyl)-N-thiazol-2-yl-propionamide (1.03 g, 3.12 mmol) in methylene chloride (31.26 mL) at 25°C was treated with a 1.0M solution of boron tribromide in methylene chloride (31.26 mL, 31.26 mmol). This solution was stirred at 25°C for 4 h. At this time, the reaction was cooled to 0°C and was then quenched by the dropwise addition of a dilute aqueous ammonium hydroxide solution.

10 The resulting solution was stirred at 0°C for 15 min. This mixture was then poured into water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide (626.8 mg, 63.4%) as a off-white solid: mp 198-200°C; EI-HRMS m/e calcd for C₁₇H₂₀N₂O₂S (M⁺) 316.1245 found 316.1256.

Example 119**4-[2-Cyclopentyl-1-(thiazol-2-ylcarbamoyl)-ethyl]-benzoic acid methyl ester**

acid (70 mg, 11.7%) as a white solid: mp 235-237°C; EI-HRMS m/e calcd for C₉H₈O₄ (M⁺) 180.0422, found 180.

A mixture of 4-carboxymethyl-benzoic acid (0.20 g, 1.11 mmol) and nickel(II) chloride hexahydrate (27 mg, 0.11 mol) in methanol (1.11 mL) was heated at 120°C for 24 h. At this time, the reaction mixture was cooled to 25°C and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 4-methoxycarbonylmethyl-benzoic acid methyl ester (66.7 mg, 28.8%) as a clear oil: EI-HRMS m/e calcd for C₁₁H₁₂O₄ (M⁺) 208.0735, found 208.0733.

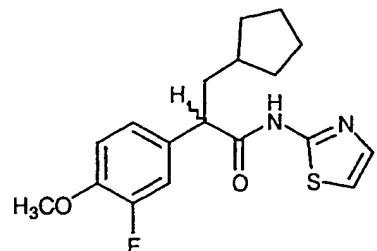
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A solution of freshly prepared lithium diisopropylamide (2.3 mL of a 0.31M stock solution, 0.71mmol) cooled to -78°C was treated with a solution of 4-methoxycarbonylmethyl-benzoic acid methyl ester (66 mg, 0.31 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (0.85 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (86 mg, 0.40 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and stirred at 25°C for 18 h. At this time, the reaction mixture was quenched by the slow addition of a saturated aqueous ammonium chloride solution (10 mL). The reaction mixture was then poured into water (50 mL). This solution was extracted into ethyl acetate (3 x 25 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 4-(2-cyclopentyl-1-methoxycarbonyl-ethyl)-benzoic acid methyl ester (60.5 mg, 65.7%) as a clear oil: EI-HRMS m/e calcd for C₁₇H₂₂O₄ (M⁺) 290.1518, found 290.1518.

A solution of 4-(2-cyclopentyl-1-methoxycarbonyl-ethyl)-benzoic acid methyl ester (0.40 g, 1.37 mmol) in tetrahydrofuran/water/methanol (13.7 mL, 3:1:1) was treated with a 1N

Example 120

3-Cyclopentyl-2-(3-fluoro-4-methoxy-phenyl)-N-thiazol-2-yl-propionamide



A solution of (3-fluoro-4-hydroxy-phenyl)-acetic acid (1.0 g, 5.87 mmol) in methanol (20 mL) was treated with a catalytic amount of sulfuric acid. The reaction was heated at 120°C for 6 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3-fluoro-4-hydroxy-phenyl)-acetic acid methyl ester (1.05 g, 97.6%) as a white solid: mp 34-36°C; EI-HRMS m/e calcd for C₉H₉FO₃ (M⁺) 184.0535, found 184.0533.

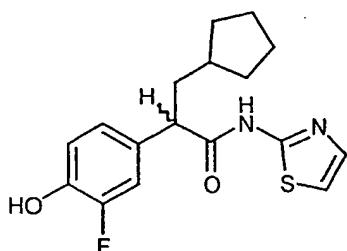
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A mixture of 3-fluoro-4-hydroxy-phenyl)-acetic acid methyl ester (1.0 g, 5.43 mmol), potassium carbonate (1.87 g, 13.57 mmol), and methyl iodide (1.12 g, 8.14 mmol) in acetone (27.1 mL) was heated at 90°C for 4 h. At this time, the potassium carbonate was removed by filtration. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded (3-fluoro-4-methoxy-phenyl)-acetic acid methyl ester (1.01 g, 94.3%) as a clear oil: EI-HRMS m/e calcd for C₁₀H₁₁FO₃ (M⁺) 198.0692, found 198.0693.

A solution of freshly prepared lithium diisopropylamide (21.6 mL of 0.31M stock solution, 6.69 mmol) cooled to -78°C was treated with a solution of (3-fluoro-4-methoxy-phenyl)-acetic acid methyl ester (1.26 g, 6.38 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (16 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.47 g, 7.02 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-fluoro-4-methoxy-phenyl)-N-thiazol-2-yl-propionamide (538.4 mg, 100%) as a white solid: mp 51-53°C; EI-HRMS m/e calcd for $C_{18}H_{21}FN_2O_2S (M^+)$ 348.1307 found 348.1312.

5

Example 121**3-Cyclopentyl-2-(3-fluoro-4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide**

A solution of 3-cyclopentyl-2-(3-fluoro-4-methoxy-phenyl)-N-thiazol-2-yl-propionamide
10 (prepared in Example 120, 305.4 mg, 0.87 mmol) in methylene chloride (8.7 mL) at 25°C
was treated with a 1.0M solution of boron tribromide in methylene chloride (8.75 mL,
8.75 mmol). This solution was stirred at 25°C for 5 h. At this time, the reaction was
cooled to 0°C and quenched by the dropwise addition of a dilute aqueous ammonium
hydroxide solution. The resulting solution was stirred at 0°C for 15 min. This mixture
15 was then poured into water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The
organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash
chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate)
afforded 3-cyclopentyl-2-(3-fluoro-4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide
199-201°C; EI-HRMS m/e calcd for
20 $C_{17}H_{19}FN_2O_2S (M^+)$ 334.1151 found 334.1152.

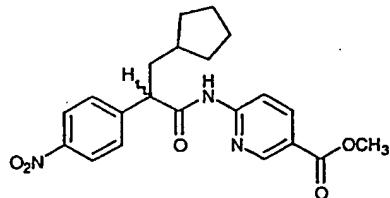
stirred at 25°C for 18 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester (151.9 mg, 19.7%) as a colorless oil: EI-HRMS m/e calcd for C₂₁H₂₃ClN₂O₃ (M⁺) 5 386.1397, found 386.1398.

A solution of 6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester (146.9 mg, 0.38 mmol) in tetrahydrofuran/water/methanol (10 mL, 3:1:1) at 25°C was treated with a 2N aqueous sodium hydroxide solution (0.4 mL, 0.80 mmol).
10 The reaction mixture was stirred at 25°C for 4 d. At this time, the reaction was concentrated *in vacuo*. The residue was diluted with water (50 mL) and extracted with diethyl ether (1 x 50 mL). The aqueous layer was acidified to pH = 1 by the dropwise addition of a 3N aqueous hydrochloric acid solution. This solution was extracted with a solution of methylene chloride/methanol (3:1, 3 x 75 mL). The organics were dried over
15 magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting solid was triturated with diethyl ether/hexanes (2:1) to afford 6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid (63.6 mg, 44.4%) as a white solid: mp 251-255°C; EI-HRMS m/e calcd for C₂₀H₂₁ClN₂O₃ (M⁺) 372.1240, found 372.1250.

20

Example 123

6-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-nicotinic acid methyl ester



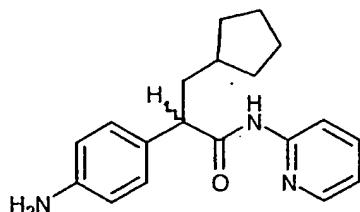
A solution of freshly prepared lithium diisopropylamide (430.55 mL of a 0.3M stock solution, 129.16 mmol) cooled to -78°C was treated with (4-nitro-phenyl)-acetic acid
25 ethyl ester (26.32 g, 125.83 mmol) in tetrahydrofuran/hexamethylphosphoramide (312.5

methyl ester (532 mg, 3.5 mmol) in tetrahydrofuran (10 mL) and *N,N*-diisopropylethylamine (0.84 mL, 4.8 mmol). This solution was stirred at 25°C for 48 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 6-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-nicotinic acid methyl ester (353.9 mg, 44.6%) as a pale orange glass: EI-HRMS m/e calcd for C₂₁H₂₃N₃O₅ (M⁺) 397.1637, found 397.1631.

Example 124

2-(4-Amino-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide

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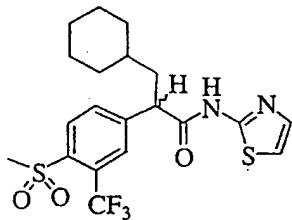
A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid (prepared in Example 22, 263 mg, 1.0 mmol) in methylene chloride (10 mL) cooled to 0°C was treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min and at 25°C for 30 min. The reaction mixture was then treated with a solution of 2-aminopyridine (200.6 mg, 2.14 mmol) in tetrahydrofuran (5 mL) and *N,N*-diisopropylethylamine (0.42 mL, 2.4 mmol). This solution was stirred at 25°C for 48 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide (138.6 mg, 40.9%) as a pale yellow glass: EI-HRMS m/e calcd for C₁₉H₂₁N₃O₃ (M⁺) 339.1581, found 339.1582.

A mixture of 3-cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide (130 mg, 0.38 mmol) in ethyl acetate (50 mL) and methanol (5 mL) was treated with a catalytic

under 60 psi of hydrogen gas in a Parr apparatus for 24 h. At this time, the catalyst was removed by filtration through a plug of celite. The filtrate was concentrated *in vacuo* to afford 6-[2-(4-amino-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester (262.8 mg, 94.7%) as a pale yellow glass: EI-HRMS m/e calcd for C₂₁H₂₅N₃O₃ (M⁺) 5 367.1895, found 367.1899.

Example 126

3-Cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide



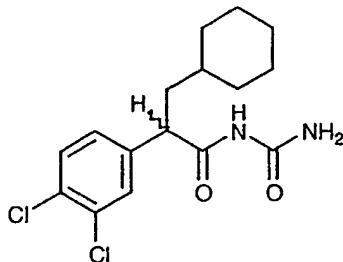
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A solution of isoamyl nitrite (4.02 mL, 30 mmol) in dimethyl disulfide (19.8 mL, 220 mmol) at 25°C was slowly treated with 4-bromo-2-(trifluoromethyl)aniline (4.8 g, 20 mmol). The reaction was exothermic with gas evolution. The resulting brown reaction mixture was heated to 80-90°C for 2 h, at which time, thin layer chromatography analysis 15 of the reaction mixture indicated the absence of starting material. The reaction mixture was cooled to 25°C and then concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (200 mL). The organic layer was washed successively with a 1N aqueous hydrochloric acid solution (1 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in* 20 *vacuo*. Biotage chromatography (FLASH 40M, Silica, 8/1 hexanes/ethyl acetate) afforded 4-bromo-1-methylsulfanyl-2-trifluoromethyl-benzene (4.73 g, 87%) as a brown oil: EI-HRMS m/e calcd for C₈H₆BrF₃S (M⁺) 269.9326, found 269.9327.

trifluoromethyl-benzene (2.12 g, 7 mmol) and the freshly prepared zinc compound in tetrahydrofuran. The resulting brick red solution was heated at 40-45°C for 2 d. The reaction mixture was cooled to 25°C and then poured into a saturated aqueous ammonium chloride solution (100 mL), and the organic compound was extracted into ethyl acetate (3 x 75 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Biotage chromatography (FLASH 40M, Silica, 9/1 to 3/1 hexanes/ethyl acetate) afforded (E)-3-cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-acrylic acid methyl ester (2.7 g, 99%) as a viscous oil: EI-HRMS m/e calcd for C₁₈H₂₁F₃O₄S (M⁺) 391.1191, found 391.1200.

A solution of nickel(II) chloride hexahydrate (36.6 mg, 0.154 mmol) and (E)-3-cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-acrylic acid methyl ester (302 mg, 0.77 mmol) in methanol (8 mL) was cooled to 0°C and then treated with sodium borohydride (87 mg, 2.29 mmol) in four portions. After the addition, the black reaction mixture was stirred for 15 min at 0°C and then allowed to warm to 25°C where it was stirred for 15 h. The black solid was filtered using filter paper and washed with methanol. The combined solvents were concentrated *in vacuo*, and the residue was diluted with ethyl acetate (50 mL). The organic layer was washed successively with a 3N aqueous hydrochloric acid solution (1 x 50 mL), a saturated aqueous sodium bicarbonate solution (1 x 50 mL) and a saturated aqueous sodium chloride solution (1 x 50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford racemic 3-cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid methyl ester (280 mg, 93%) as a viscous oil: EI-HRMS m/e calcd for C₁₈H₂₃F₃O₄S (M⁺) 392.1269, found 392.1276.

A solution of 3-cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid methyl ester (265 mg, 0.67 mmol) in ethanol (5 mL) was treated with a 1N aqueous sodium hydroxide solution (1.5 mL). The solution was heated at 45-50°C for 5 h, at

Example 127**(A) 3-Cyclohexyl-2-(3,4-dichloro-phenyl)-propionyl]-urea**

5 A solution of (3,4-dichloro-phenyl)-acetic acid (14.0 g, 0.068 mol) in methanol (71mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 12 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3,4-dichloro-phenyl)-acetic acid methyl ester (15.0 g, quant.) as a white solid: mp 30-32°C; EI-HRMS m/e calcd for C₉H₈Cl₂O₂ (M⁺) 217.9901, found 217.9907.

A solution of freshly prepared lithium diisopropylamide (16.3 mL of a 0.31M stock solution, 5.04 mmol) cooled to -78°C was treated with (3,4-dichloro-phenyl)-acetic acid methyl ester (1.0 g, 4.58 mmol) in tetrahydrofuran/hexamethylphosphoramide (8.6 mL, 15 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of bromomethylcyclohexane (1.92 mL, 13.76 mmol) in hexamethylphosphoramide (1 mL). The reaction mixture was stirred at -78°C for 3 h. The reaction was warmed to 25°C and stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (20 mL). This mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 3-cyclohexyl-2-(3,4-dichloro-phenyl)-propionic acid

(f) From 3-cyclohexyl-2-(3,4-dichloro-phenyl)-propionic acid methyl ester and methyl urea: [3-Cyclohexyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea as a white solid: mp 69-73°C; EI-HRMS m/e calcd for $C_{17}H_{22}Cl_2N_2O_2 (M^+)$ 356.1058, found 356.1046.

(g) From 1-[2-(3,4-dichloro-phenyl)-4-methyl-pentanoyl]-3-methyl ester and methyl-urea:

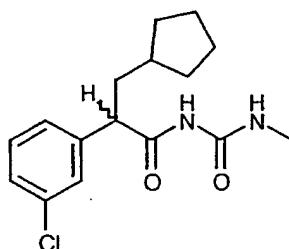
5 1-[2-(3,4-Dichloro-phenyl)-4-methyl-pentanoyl]-3-methyl-urea as a white solid: mp 123-125°C; EI-HRMS m/e calcd for $C_{14}H_{18}Cl_2N_2O_2 (M^+)$ 316.0745, found 316.0740.

(h) From 2-(3,4-dichloro-phenyl)-hexanoic acid methyl ester and methyl-urea: 1-[2-(3,4-Dichloro-phenyl)-hexanoyl]-3-methyl-urea as a clear oil: EI-HRMS m/e calcd for $C_{14}H_{18}Cl_2N_2O_2 (M^+)$ 316.0743, found 316.0745.

10

Example 128

1-[2-(3-Chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



(3-Chloro-phenyl)-acetic acid (6.03 g, 0.03 mol) was dissolved in ethanol (37.7 mL) and 15 treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 12 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3-chloro-phenyl)-acetic acid ethyl ester (6.10 g, 86.8%) as a clear oil: EI-HRMS m/e calcd for $C_{10}H_{11}ClO_2 (M^+)$ 198.0448, found 198.0442.

20

A solution of freshly prepared lithium diisopropylamide (23 mL of 0.31M stock solution, 7.13 mmol) cooled to -78°C was treated with (3-chloro-phenyl)-acetic acid ethyl ester (1.28 g, 6.48 mmol) in tetrahydrofuran/hexamethylphosphoramide (16.1 mL, 3:1). The

A solution of (3,4-difluoro-phenyl)-acetic acid (5.0 g, 0.029 mol) in methanol (30.0 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 4 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3,4-difluoro-phenyl)-acetic acid methyl ester (5.15 g, 95.2%) as a clear oil: EI-HRMS m/e calcd for $C_9H_8F_2O_2$ (M^+) 186.0493, found 186.0492.

A solution of freshly prepared lithium diisopropylamide (23.0 mL of a 0.31M stock solution, 7.13 mmol) cooled to -78°C was treated with (3,4-difluoro-phenyl)-acetic acid 10 methyl ester (1.20 g, 6.48 mmol) in tetrahydrofuran/hexamethylphosphoramide (16.1 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.50 g, 7.13 mmol) in hexamethylphosphoramide (1 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. The reaction 15 mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (20 mL). This mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-difluoro-phenyl)-propionic acid 20 methyl ester (1.79 g, quant.) as a clear oil: EI-HRMS m/e calcd for $C_{15}H_{18}F_2O_2$ (M^+) 268.1275, found 268.1278.

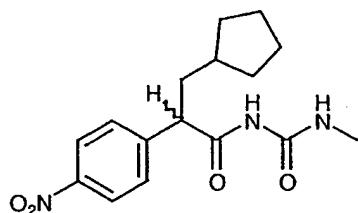
A mixture of 3-cyclopentyl-2-(3,4-difluoro-phenyl)-propionic acid methyl ester (1.65 g, 6.14 mmol) and methyl urea (683 mg, 9.22 mmol) in a solution of magnesium methoxide 25 in methanol (7.4 wt%, 16.6 mL, 12.3 mmol) was refluxed at 100°C for 8 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(3,4-difluoro-phenyl)-propionyl]-3-methyl-urea (180 mg, 9.4%) as a white solid: mp 111-113°C; EI-HRMS m/e calcd for $C_{16}H_{20}F_2N_2O_2$ (M^+) 310.1493, found 310.1499.

A mixture of 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid ethyl ester (1.65 g, 5.89 mmol) and methyl urea (654 mg, 8.83 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 16.9 mL, 11.78 mmol) was refluxed at 100°C for 6 h. The reaction
5 mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 1-[2-(4-chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea (105.3 mg, 5.8 %) as a white solid: mp 145-147°C; EI-HRMS m/e calcd for C₁₆H₂₁ClN₂O₂(M⁺) 308.1292, found 308.1291.

10

Example 131

1-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionyl]-3-methyl-urea



A solution of freshly prepared lithium diisopropylamide (430.55 mL of a 0.3M stock solution, 129.16 mmol) cooled to -78°C was treated with (4-nitro-phenyl)-acetic acid
15 ethyl ester (26.32 g, 125.83 mmol) in tetrahydrofuran/hexamethylphosphoramide (312.5 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (27.75 g, 132.1 mmol) in hexamethylphosphoramide (27.8 mL). The mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture
20 was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (250 mL). The reaction mixture was concentrated *in vacuo*. The residue was diluted with water (250 mL) and extracted with ethyl acetate (3 x 300 mL). The organics were washed with a saturated aqueous lithium chloride solution (2 x 250 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck
25 Silica gel 60, 230-400 mesh, 95/5 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-

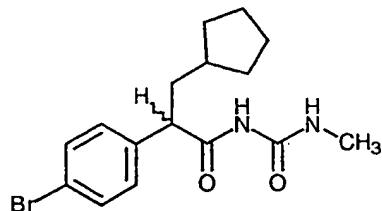
lithium chloride solution (2 x 50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 95/5 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-phenyl-propionic acid ethyl ester (1.70 g, quant.) as a pale yellow oil: EI-HRMS m/e calcd for C₁₆H₂₂O₂ (M⁺) 247.1698, found 5 247.1704.

A mixture of 3-cyclopentyl-2-phenyl-propionic acid ethyl ester (1.70 g, 7.06 mmol) and methyl urea (1.04 mg, 14.13 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 130.3 mL, 21.18 mmol) was refluxed at 100°C for 24 h. The reaction mixture 10 was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 1-(3-cyclopentyl-2-phenyl-propionyl)-3-methyl-urea (1.21 mg, 62.4 %) as a white solid: mp 145-147°C; EI-HRMS m/e calcd for C₁₆H₂₂N₂O₂ (M⁺) 274.1681, found 274.1682.

15

Example 133

1-[2-(4-Bromo-phenyl)-3-cyclopentyl-propionyl]-3-methyl urea



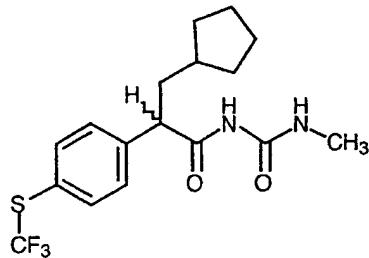
A solution of diisopropylamine (7.7 mL, 54.88 mmol) in dry tetrahydrofuran (23 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL) was cooled to -78°C under 20 nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (22.0 mL, 54.88 mmol). The reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-bromophenylacetic acid (5.62 g, 26.13 mmol) in dry tetrahydrofuran (23 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 1 h,

230 mesh, 3/1 hexanes/ethyl acetate) afforded 1-[2-(4-bromo-phenyl)-3-cyclopentyl-propionyl]-3-methyl urea (58.7 mg, 12%) as a white solid: mp 184-186°C; EI-HRMS m/e calcd for C₁₆H₂₁BrN₂O₂ (M⁺) 352.0786, found 352.0791.

5

Example 134

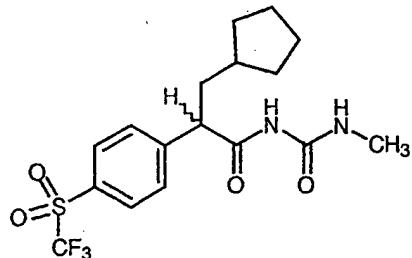
1-[3-Cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)-propionyl]-3-methyl urea



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C
 10 under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at
 15 which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted
 20 with ethyl acetate (1 x 300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-

Example 135

1-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionyl]-3-methyl urea



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL)

5 and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfonyl-phenyl)propionic acid (1.47 g, 58%) as a cream solid: mp 69-71°C; EI-HRMS m/e calcd for $\text{C}_{15}\text{H}_{17}\text{F}_3\text{O}_2\text{S} (\text{M}^+)$ 318.0901, found 318.0912.

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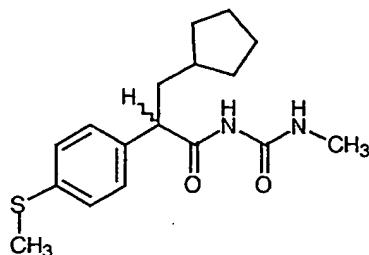
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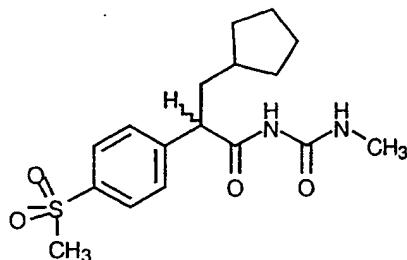
A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfonyl-phenyl)propionic acid (1.33 g, 4.18 mmol) in methanol (10 mL) was treated slowly with 4 drops of concentrated sulfuric

mixture was then heated under reflux for 2 d. The reaction mixture was allowed to cool to 25°C and then filtered through celite. The celite was thoroughly washed with ethyl acetate until the solvent passing through the celite showed absence of desired product by thin layer chromatography. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 5 1-[3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionyl]-3-methyl urea (119.3 mg, 28%) as a white solid: mp 191-192°C; FAB-HRMS m/e calcd for C₁₇H₂₁F₃N₂O₄S (M+H)⁺ 407.1252, found 407.1247.

10

Example 136**1-[3-Cyclopentyl-2-(4-methylsulfanyl-phenyl)-propionyl]-3-methyl urea**

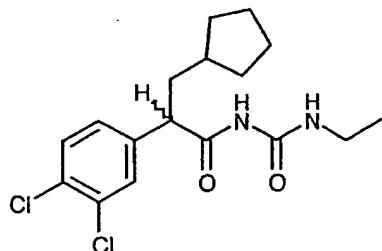
A solution of diisopropylamine (3.2 mL, 23.16 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL) was cooled to -78°C 15 under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (2.3 mL, 23.16 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(methylthio)phenylacetic acid (2.01 g, 11.03 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL). The reaction mixture was allowed to stir at -78°C for 1 h, at 20 which time, a solution of iodomethylcyclopentane (2.55 g, 12.13 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred at -78°C for 30 min and then allowed to warm to 25°C where it was stirred for 24 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10%

Example 137**1-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionyl]-3-methyl urea**

5 A solution of diisopropylamine (3.3 mL, 23.5 mmol) in dry tetrahydrofuran (50 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (2.35 mL, 23.5 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-methylsulfonylphenylacetic acid (2.40 g, 11.2 mmol) in a small amount of dry tetrahydrofuran. After approximately one-half of the 4-methylsulfonylphenylacetic acid in dry tetrahydrofuran was added, a precipitate formed. Upon further addition of the remaining 4-methylsulfonylphenylacetic acid in dry tetrahydrofuran, the reaction mixture became thick in nature. After complete addition of the 4-methylsulfonylphenylacetic acid in dry tetrahydrofuran, the reaction mixture was 15 very thick and became difficult to stir. An additional amount of dry tetrahydrofuran (20 mL) was added to the thick reaction mixture, and the reaction mixture was stirred at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (2.35 g, 11.2 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture 20 was quenched with water (100 mL), and the resulting yellow reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The aqueous residue was acidified to pH = 2 using concentrated hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ethyl

Example 138

(A) 1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea



A solution of triphenylphosphine (28.80 g, 109.8 mmol) and imidazole (14.9 g, 219.6 mmol) in methylene chloride (160 mL) was cooled to 0°C and then slowly treated with iodine (27.87 g, 109.8 mmol). The reaction mixture was then treated dropwise with a solution of cyclopentylmethanol (10.0 g, 99.8 mmol) in methylene chloride (10 mL). The resulting reaction mixture was allowed to warm to 25°C, where it was stirred for 4 h. The reaction mixture was then diluted with water (50 mL), and the reaction mixture was further extracted with methylene chloride (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* at 25°C. The resulting solid was washed with pentane (4 x 50 mL) and filtered through a silica gel plug. The filtrate was concentrated *in vacuo* at 25°C to afford iodomethylcyclopentane (18.48 g, 88%) as a clear colorless liquid: EI-HRMS m/e calcd for C₆H₁₁I (M⁺) 209.9906, found 15 209.9911.

A solution of diisopropylamine (13.36 mL, 101.89 mmol) in tetrahydrofuran (250 mL) was cooled to -78°C under a nitrogen atmosphere and then treated with a 2.0M solution of *n*-butyllithium in hexanes (51 mL, 101.89 mmol). The reaction mixture was stirred at -20 78°C for 15 min, at which time, a solution of 3,4-dichlorophenyl acetic acid (9.08 g, 44.3 mmol) in tetrahydrofuran (60 mL) and hexamethylphosphoramide (20 mL) was slowly added via a cannula. The bright yellow solution was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (11.17 g, 53.2 mmol) in hexamethylphosphoramide (10 mL) was added via a cannula. The reaction mixture was

afforded 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea (29 mg, 26%) as a white foam: EI-HRMS m/e calcd for $C_{17}H_{22}Cl_2N_2O_2$ (M^+) 356.1058, found 356.1066.

5 (B) In an analogous manner, there were obtained:

(a) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and isopropyl isocyanate:

1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-isopropyl-urea as a white solid:

mp 134.6-138.3°C; EI-HRMS m/e calcd for $C_{18}H_{24}Cl_2N_2O_2$ (M^+) 370.1215, found

370.1232.

10 (b) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and propyl isocyanate: 1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-propyl-urea as a white solid: mp 117.8-120°C; EI-HRMS m/e calcd for $C_{18}H_{24}Cl_2N_2O_2$ (M^+) 370.1215, found 370.1209.

(c) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and ethyl 3-isocyanatopropionate: 3-{3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid ethyl ester as a light yellow oil: EI-HRMS m/e calcd for $C_{20}H_{26}Cl_2N_2O_4$ (M^+) 428.1270, found 428.1265.

(d) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and ethyl isocyanatoacetate: {3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester as a light yellow oil: EI-HRMS m/e calcd for $C_{19}H_{24}Cl_2N_2O_4$ (M^+) 414.1113, found 414.1108.

(e) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and allyl isocyanate: 1-Allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea as a clear colorless oil: EI-HRMS m/e calcd for $C_{18}H_{22}Cl_2N_2O_2$ (M^+) 368.1058, found 368.1064.

74.6°C; $[\alpha]^{23}_{589} = -27.6^\circ$ (c=0.188, chloroform); EI-HRMS m/e calcd for $C_{20}H_{25}Cl_2NO_3$ (M^+) 397.1211, found 397.1212.

A solution of 3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-4(S)-isopropyl-
5 oxazolidin-2-one (1.88 g, 4.72 mmol) in tetrahydrofuran (73 mL) and water (22 mL)
cooled to 0°C was treated with a 30% aqueous hydrogen peroxide solution (2.1 mL) and
lithium hydroxide (394 mg, 9.4 mmol). The reaction was stirred at 0°C for 1 h. At this
time, the reaction was quenched with a saturated aqueous sodium sulfite solution (16 mL)
followed by the addition of an aqueous solution of 0.5N sodium bicarbonate (50 mL).
10 The tetrahydrofuran was then removed *in vacuo*. The residue was diluted with water (40
mL) and extracted with methylene chloride (3 x 20 mL). The aqueous layer was then
acidified to pH = 2 with a 5N aqueous hydrochloric acid solution and extracted with ethyl
acetate (4 x 25 mL). The ethyl acetate layers were then dried over sodium sulfate,
filtered, and concentrated *in vacuo* to afforded of 3-cyclopentyl-2(R)-(3,4-dichloro-
15 phenyl)-propionic acid (928 mg, 70%) as a white solid: mp 75.1-78.3°C; $[\alpha]^{23}_{589} = -50.3^\circ$
(c=0.100, chloroform); EI-HRMS m/e calcd for $C_{14}H_{16}Cl_2O_2$ (M^+) 286.0527, found
286.0535.

A solution of 3-cyclopentyl-2(R)-(3,4-dichlorophenyl)-propionic acid (105 mg, 0.37
20 mmol) in methylene chloride (10 mL) and 1 drop of *N,N*-dimethylformamide was cooled
to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride
(0.18 mL, 0.37 mmol). The reaction was stirred for 30 min at 0°C, at which time,
1,1,1,3,3-hexamethyldisilazane (0.25 mL, 1.17 mmol) was added to the reaction
mixture. The reaction was then allowed to slowly warm to 25°C and stirred at 25°C for
25 16h. The reaction mixture was then washed with a 5% aqueous sulfuric acid solution (2 x
10 mL). The combined aqueous layers were extracted with methylene chloride (3 x 10
mL). The combined organic layers were washed with a saturated aqueous sodium
chloride solution (1 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in*
vacuo. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 60/40 hexanes/ethyl

89%) as a yellow oil: EI-HRMS m/e calcd for $C_9H_8ClNO_4$ (M^+) 229.0142, found 229.0146.

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and
5 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and then treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min
10 period. The reaction mixture turned deep purple (almost black) in color. The reaction mixture was then stirred at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was then stirred at -78°C and then allowed to warm to 25°C, where it was stirred for 48 h. The reaction mixture was quenched with a
15 saturated aqueous ammonium chloride solution (50 mL), and the resulting reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue was diluted with ethyl acetate (150 mL) and water (50 mL). The organic phase was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400
20 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (2.17 g, 32%) as a yellow oil: EI-HRMS m/e calcd for $C_{15}H_{18}ClNO_4$ (M^+) 311.0924, found 311.0927.

A solution of 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (1.00
25 g, 3.21 mmol) and sodium methanesulfinate (0.36 g, 3.53 mmol) in dimethyl sulfoxide (3 mL) was heated at 130°C for 5 h. The black reaction mixture was then poured over ice (20 g), resulting in the formation of a brown sticky substance. The resulting mixture was then diluted with ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined

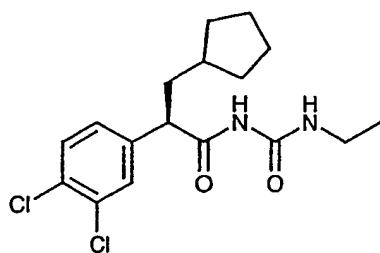
Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionamide (140 mg, 47%) as a yellow foam: mp 72-76°C (foam to gel); FAB-HRMS m/e calcd for $C_{15}H_{20}N_2O_5S$ ($M+H$)⁺ 341.1172, found 341.1181.

5

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionamide (126 mg, 0.37 mmol) and methyl isocyanate (211 mg, 3.70 mmol) in toluene (2 mL) was heated under reflux (120°C) for 15 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo*. The resulting yellow oil was treated with a small amount of a
10 1/1 mixture of hexanes/ethyl acetate, and a precipitate started to form. The material was further cooled in the freezer for 2 h to facilitate additional precipitation. The solid was collected by filtration and then dried *in vacuo* to afford 1-[3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionyl]-3-methyl-urea (50 mg, 35%) as a pale yellow solid: mp 241-242°C; FAB-HRMS m/e calcd for $C_{17}H_{23}N_3O_6S$ ($M+H$)⁺ 398.1386, found
15 398.1399.

Example 141

1-[3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea



20 A solution of 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide (prepared in Example 139, 103 mg, 0.36 mmol) in toluene (10 mL) was treated with ethyl isocyanate (40 µL, 0.54 mmol). The resulting reaction mixture was heated under reflux for 24 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2(R)-

and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 2-(4-chloro-phenyl)-4-methyl-pentanoic acid ethyl ester (1.24 g, 87.1%) as a white solid: mp 34-35°C; EI-HRMS m/e calcd for C₁₄H₁₉ClO₂ (M⁺) 254.1074, found 254.1069.

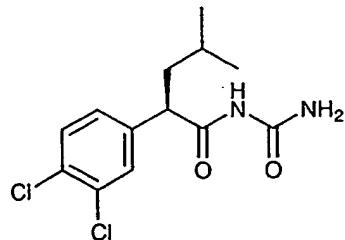
5

A mixture of 2-(4-chloro-phenyl)-4-methyl-pentanoic acid ethyl ester (508 mg, 1.99 mmol) and urea (239 mg, 3.99 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 4.28 mL, 2.99 mmol) was heated to reflux for 24 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 10 50/50 hexanes/ethyl acetate) afforded [2-(4-chloro-phenyl)-4-methyl-pentanoyl]-urea (28.1 mg, 5.2%) as a white solid: mp 164-165°C; EI-HRMS m/e calcd for C₁₃H₁₇CIN₂O₂ (M⁺) 268.0979, found 268.0972.

Example 143

15

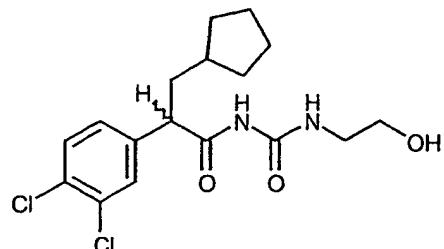
R-[2-(3,4-Dichloro-phenyl)-4-methyl-pentanoyl]-urea



A solution of (3,4-dichloro-phenyl)-acetic acid (10.0 g, 0.048 mol) in ethanol (50 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 7 h. The reaction was concentrated *in vacuo*, diluted with diethyl ether, and poured 20 into water. The ether layer was washed with a saturated aqueous sodium bicarbonate solution and water. The organics were then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Vacuum distillation (bath temperature: 175°C; head temperature: 125°C) afforded (3,4-dichloro-phenyl)-acetic acid ethyl ester (9.38 g, 82.5%) as a clear oil: EI-HRMS m/e calcd for C₁₀H₁₀Cl₂O₂ (M⁺) 232.0058, found 232.0066.

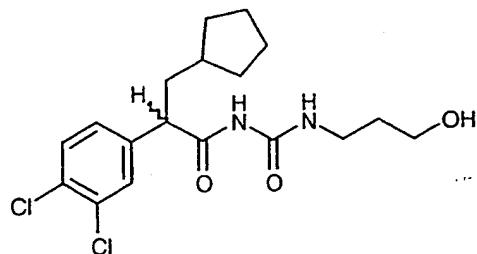
Example 144

1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea



A solution of 1-allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea (prepared
5 in Example 12B-e, 75 mg, 0.20 mmol) in dry methylene chloride (10 mL) and methanol
(2 drops, needed to solubilize the compound) was cooled to -78°C and deoxygenated by
bubbling argon through the reaction mixture. Ozone was then generated and bubbled
through the reaction until a blue color appeared and then the reaction was stirred for five
min.

10 At this time, argon was bubbled through the solution again until the blue color
disappeared. Triphenylphosphine (54 mg, 0.20 mmol) was then added and the reaction
warmed to 25°C and stirred for 16 h. At this time, the reaction was concentrated *in*
vacuo and then dissolved in dry methanol (10 mL). The reaction was cooled to 0°C and
then slowly treated with sodium borohydride (31 mg, 0.81 mmol). The reaction was then
15 warmed to 25°C and stirred for 1 h. It was then quenched with water (10 mL) and
extracted with ethyl acetate (3 x 15 mL). The organics were combined and washed with
water (1 x 15 mL), a saturated aqueous sodium chloride solution (1 x 15 mL), dried over
sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica
20 gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(3,4-
dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea (48 mg, 64%) as a hygroscopic
white solid: EI-HRMS m/e calcd for C₁₇H₂₂Cl₂N₂O₃ (M⁺) 370.1215, found 370.1209.

Example 146**1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea**

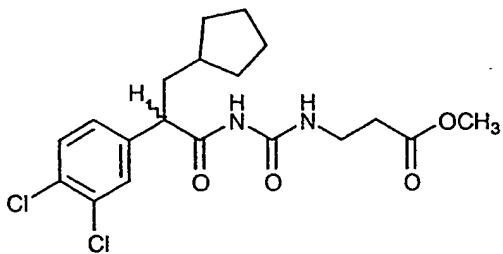
A solution of 1-allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea (prepared in Example 12B-e, 132 mg, 0.36 mmol) in tetrahydrofuran (10 mL) cooled to 0°C was treated with a 1M solution of borane-tetrahydrofuran (0.7 mL, 0.72 mmol). The reaction mixture was allowed to slowly warm from 0°C to 25°C over 1 h.. At this time, the solution was re-cooled to 0°C and ethanol (2 mL) followed by a mixture of a saturated aqueous sodium bicarbonate solution (6 mL) and 30% hydrogen peroxide (2 mL) was added slowly. This mixture was allowed to slowly warm to 25°C while stirring for 1 h. At this time, the reaction was re-cooled to 0°C and slowly quenched with a saturated aqueous sodium sulfite solution (20 mL). This solution was extracted with ethyl acetate (3 x 20 mL). The organics were washed with a saturated aqueous sodium chloride solution (1 x 15 mL), dried over sodium sulfate, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) effected the separation of two spots, the second of the two product spots to elute off the column afforded 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea (73 mg, 53%) as a white hygroscopic solid: EI-HRMS m/e calcd for C₁₈H₂₄Cl₂N₂O₃ (M⁺) 386.1164, found 386.1172.

afforded {3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid methyl ester (21 mg, 68%) as a white solid: mp 134.5-136.6°C; EI-HRMS m/e calcd for C₁₈H₂₂Cl₂N₂O₄ (M⁺) 400.0957, found 400.0970.

5

Example 148

**3-{3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid
methyl ester**



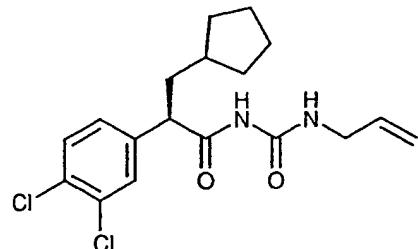
A solution of 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid ethyl ester (prepared in Example 12B-c, 94 mg, 0.22 mmol) in ethanol (5 mL) at 10 25°C was treated with a solution of potassium hydroxide (43 mg, 0.77 mmol) in water (1 mL). This solution was stirred at 25°C for 2 h. At this time, the reaction was diluted with water (5 mL) and the ethanol was removed *in vacuo*. The aqueous layer was acidified to pH = 2 with a 1N aqueous hydrochloric acid solution and extracted with methylene 15 chloride (3 x 15 mL). The organic layers were then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate plus 1% acetic acid) afforded 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid (30 mg, 35%) as a white foam: FAB-HRMS m/e calcd for C₁₈H₂₂Cl₂N₂O₄ (M+H)⁺ 401.1035, found 401.1022.

20

A solution of 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid (20 mg, 0.05 mmol) in methanol (5 mL) was treated with concentrated sulfuric acid (4 drops). This solution was heated to 80°C for 8 h. At this time, the reaction was cooled to 25°C and diluted with water (10mL). This solution extracted with ethyl acetate (3 x 20

Example 150

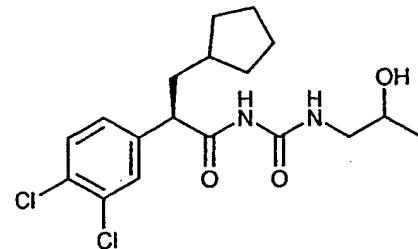
1-Allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea



A solution of 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide (prepared in Example 13, 1.02 g, 3.55 mmol) in toluene (30 mL) was treated with allyl isocyanate (0.47 mL, 5.33 mmol). This solution was heated to reflux for 16 h. At this time, the reaction was cooled to 25°C and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 1-allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea (1.06 g, 81%) as a colorless oil:
 10 [α]²³₅₈₉ = -25.2° (c=0.151, chloroform); EI-HRMS m/e calcd for C₁₈H₂₂Cl₂N₂O₂ (M⁺) 368.1058, found 368.1054.

Example 151

1-[3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea



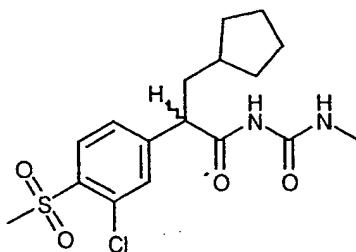
A solution of 1-allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea (prepared in Example 24, 765 mg, 2.07 mmol) in tetrahydrofuran (50 mL) cooled to 0°C was treated with a 1.0M borane solution in tetrahydrofuran (4.14 mL, 4.14 mmol). The reaction was allowed to warm from 0°C to 25°C over 1 h. At this time, the reaction was

vacuo. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea (173 mg, 22%) as a white foam: $[\alpha]^{23}_{589} = -37.3^\circ$ ($c=0.075$, chloroform); EI-HRMS m/e calcd for $C_{18}H_{24}Cl_2N_2O_3$ (M^+) 386.1164, found 386.1154.

5

Example 153

1-[2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



A solution of aluminum trichloride (34.8 g, 261.4 mmol) in chloroform (120 mL) cooled to 0°C was treated with a solution of ethyl chlorooxoacetate (18.7 mL, 167.5 mmol) in chloroform (120 mL). The mixture was stirred at 0°C for 30 min. At this time, a solution of 2-chlorothioanisole (25.0 g, 156.5 mmol) in chloroform (120 mL) was added dropwise to the reaction mixture. It was then allowed to warm to 25°C and stirred for an additional 3.5 h at 25°C. At this time, the reaction was quenched by the slow addition of water (500 mL) and extracted with chloroform (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded (3-chloro-4-methysulfanyl-phenyl)-oxo-acetic acid ethyl ester (31.37 g, 77%) as a yellow oil: EI-HRMS m/e calcd for $C_{18}H_{24}Cl_2N_2O_3$ (M^+) 386.1164, found 386.1154.

20

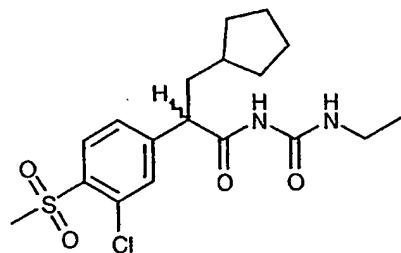
A solution of cyclopentylmethyl triphenylphosphonium iodide (prepared in Example 33, 725 mg, 1.53 mmol) in tetrahydrofuran (10 mL) cooled to 0°C was treated with a 1.0M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (2.14 mL, 2.14 mmol).

concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded a mixture of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester (transesterification occurred under the reaction conditions) (937 mg) as a clear colorless oil. (Transesterification occurred under the reaction conditions and the mixture of esters was carried on without characterization)

A solution of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid 10 ethyl ester (268 mg) and methyl urea (110 mg, 1.5 mmol) in magnesium methoxide in methanol (7.4 wt%, 1.6 mL, 1.1 mmol) was heated to 100°C for 8 h. At this time, the reaction was concentrated *in vacuo*. The residue was then dissolved in ethyl acetate (50 mL), filtered through a plug of silica gel, and washed with ethyl acetate (100 mL). The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 15 mesh, 60/40 hexanes/ethyl acetate) afforded 1-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea (55 mg, 19% yield) as a white foam: FAB-HRMS m/e calcd for C₁₇H₂₃ClN₂O₄S (M+H)⁺ 387.1145, found 387.1156.

Example 154

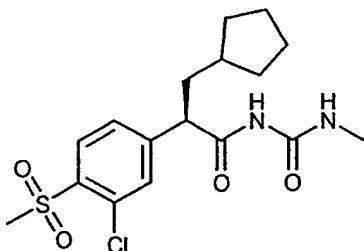
20 1-[2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-ethyl-urea



A solution of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester (prepared in Example 27, 937 mg) in ethanol (30 mL) at 25°C was treated with

Example 155

**1-[2(R)-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl
urea**



5 A solution of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 28, 6.1 g, 18.3 mmol), (R)-(+)-4-benzyl-2-oxazolidinone (2.83g, 15.9 mmol), triethylamine (6.68 mL, 47.7 mmol), in toluene (50 mL) heated to 80°C was treated with pivaloyl chloride (3.55 mL, 28.8 mmol) in toluene (10 mL). The resulting slurry was heated at 80°C for 36 h. At this time, the reaction was cooled to 20°C and 10 concentrated *in vacuo*. The residue was diluted with ethyl acetate (150 mL) washed with a 1N aqueous hydrochloric acid solution (100 mL), a 10% aqueous sodium carbonate solution (100 mL), and a saturated aqueous sodium chloride solution (100 mL). The organics were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/5/5 methylene 15 chloride/hexanes/ethyl acetate) afforded 4(R)-benzyl-3-[2(S)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-oxazolidin-2-one (2.08 g, 23%) as a white foam: $[\alpha]^{23}_{589} = +10.4^\circ$ ($c=0.144$, chloroform); FAB-HRMS m/e calcd for $C_{25}H_{28}ClNO_5S$ ($M+H$)⁺ 490.1455, found 490.1457 and 4(R)-benzyl-3-[2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-oxazolidin-2-one (2.20 g, 25%) as a 20 white foam: $[\alpha]^{23}_{589} = -93.9^\circ$ ($c=0.165$, chloroform); FAB-HRMS m/e calcd for $C_{25}H_{28}ClNO_5S$ ($M+H$)⁺ 490.1455, found 490.1443.

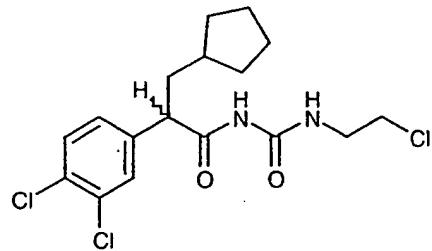
A solution of lithium hydroxide (215 mg, 9.0 mmol) in water (2.8 mL) was treated with a 30% aqueous solution of hydrogen peroxide (2.0 mL, 18 mmol). This lithium

1.94 mmol). The reaction mixture was then heated at 100°C for 16 h. At this time, the reaction was concentrated *in vacuo*. Biotage chromatography (FLASH 40S, Silica, 60/40 hexanes/ethyl acetate) afforded 1-[2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea (79 mg, 42%) as a white foam: $[\alpha]_{D}^{25} = -8.9^\circ$ ($c=0.09$, chloroform); FAB-HRMS m/e calcd for $C_{17}H_{23}ClN_2O_4S$ ($M+H$)⁺ 387.1145, found 387.1142.

Example 156

1-(2-Chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionyl]-urea

10



A solution of 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide (prepared in Example 12, 182 mg, 0.64 mmol) in toluene (10 mL) was treated with 2-chloroethyl isocyanate (0.08 mL, 0.95 mmol). The reaction was heated at reflux for 16 h. At this time, the reaction was cooled to 25°C and concentrated *in vacuo*.

Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 1-(2-chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionyl]-urea (189 mg, 76%) as a colorless oil: EI-HRMS m/e calcd for $C_{17}H_{21}Cl_3N_2O_2$ (M^+) 390.0669, found 390.0659.

concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 8/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-trifluoromethylsulfanyl-phenyl)-propionic acid methyl ester (2.95 g, 89%) as a colorless oil: EI-HRMS m/e calcd for $C_{16}H_{19}F_3O_2S (M^+)$ 332.1058, found 332.1047.

5

A solution of 3-cyclopentyl-2-(3-trifluoromethylsulfanyl-phenyl)-propionic acid methyl ester (2.75 g, 8.27 mmol) in methylene chloride (30 mL) was treated with 3-chloroperoxybenzoic acid (80-85% grade, 4.28 g based on 80%, 20.67 mmol). The reaction mixture was stirred at 25°C for 6 h. At this time, thin layer chromatography 10 showed the presence of two new lower R_f products. An additional 4.00 g of 3-chloroperoxybenzoic acid was added to the reaction mixture to drive the conversion of the sulfoxide to the sulfone, and the resulting reaction mixture was stirred at 40°C for 3 d. The reaction mixture was cooled to 25°C and then partitioned between water (100 mL) and methylene chloride (100 mL). The layers were shaken and separated. The organic 15 phase was washed twice with a saturated aqueous sodium bicarbonate solution, washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/methylene chloride) afforded 3-cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionic acid methyl ester (2.07 g, 69%) as a colorless oil: EI-HRMS m/e calcd for $C_{16}H_{19}F_3O_4S (M^+)$ 364.0956, 20 found 364.0947.

3-Cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionic acid methyl ester (500 mg, 1.37 mmol) and methyl urea (305 mg, 4.12 mmol) were treated with a solution of magnesium methoxide in methanol (7.4 wt%, 5.9 mL, 4.12 mmol). The reaction mixture 25 was then concentrated *in vacuo* to approximately one-half the volume of methanol. The resulting reaction mixture was then heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C, diluted with ethyl acetate (10 mL), and then filtered through celite. The celite was thoroughly washed with ethyl acetate. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1

quenched with a saturated aqueous ammonium chloride solution (10 mL) and then partitioned between water (75 mL) and ethyl acetate (75 mL). The layers were shaken and separated. The aqueous layer was further extracted with ethyl acetate (75 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution,

5 dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 5/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-propionic acid methyl ester (2.69 g, 83%) as a colorless oil: EI-HRMS m/e calcd for C₁₆H₁₈F₄O₂ (M⁺) 318.1243, found 318.1250.

10 3-Cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-propionic acid methyl ester (750 mg, 2.36 mmol) and methyl urea (437 mg, 5.90 mmol) were treated with a solution of magnesium methoxide in methanol (7.4 wt%, 14.5 mL, 7.08 mmol). The reaction mixture was then concentrated *in vacuo* to approximately one-half the volume of methanol. The resulting reaction mixture was then heated under reflux for 15 h. The

15 reaction mixture was allowed to cool to 25°C and then partitioned between water (75 mL) and ethyl acetate (75 mL). An emulsion formed, and a saturated aqueous sodium chloride solution was added to break down the emulsion. The aqueous layer was further extracted with ethyl acetate (2 x 75 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a white semi-solid. The semi-solid

20 was treated with a solution of 2/1 hexanes/ethyl acetate, and a white solid formed. The solid was filtered, washed well with hexanes, and dried to afford 1-[3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-propionyl]-3-methyl-urea (322 mg, 38%) as a white solid: mp 187-189°C; FAB-HRMS m/e calcd for C₁₇H₂₀F₄N₂O₂ (M+H)⁺ 361.1539, found 361.1549.

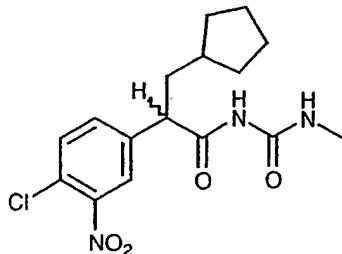
86%) as a light orange solid: mp 195-198°C; FAB-HRMS m/e calcd for C₂₄H₂₆P (M+H)⁺ 345.1772, found 345.1784.

A suspension of cyclopentylmethyl triphenylphosphonium iodide (24.48 g, 51.82 mmol) 5 in tetrahydrofuran (100 mL) cooled to 0°C was treated dropwise with a 1.0M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (52 mL, 51.82 mmol). The bright orange reaction mixture was stirred at 0°C for 1 h. The reaction mixture was then treated with (4-ethylsulfanyl-phenyl)-oxo-acetic acid ethyl ester (9.50 g, 39.87 mmol). The resulting reaction mixture was allowed to warm to 25°C where it was stirred for 20 h. 10 The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then diluted with water (300 mL). The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl 15 acetate) afforded the 3-cyclopentyl-2-(4-ethylsulfanyl-phenyl)-acrylic acid ethyl ester (6.08 g, 50%) as a yellow oil containing a 1.82:1 mixture of E:Z isomers: FAB-LRMS m/e calcd for C₁₈H₂₄O₂S (M+H)⁺ integer mass 304, found 305.

A solution of 3-cyclopentyl-2-(4-ethylsulfanyl-phenyl)-acrylic acid ethyl ester [5.76 g, 20 18.92 mmol, E:Z = 1.82:1] in methylene chloride (47 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 11.45 g based on 57%, 37.83 mmol). The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate 25 solution (3 x 200 mL), washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-acrylic acid ethyl ester (4.89 g, 77%) as a

Example 160

1-[2-(4-Chloro-3-nitro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



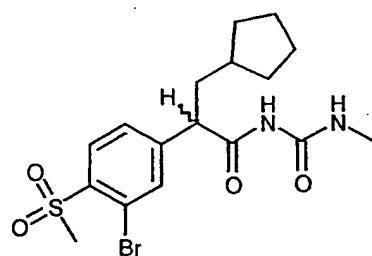
5 A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitro-phenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS m/e calcd for C₉H₈ClNO₄ (M⁺) 229.0142, found 229.0146.

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and 15 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) cooled to -78°C was treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 min. At this time, the reaction was treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min period. The 20 reaction mixture turned deep purple (almost black) in color. The reaction mixture was then stirred at -78°C for 1 h. At this time, the reaction was treated with a solution of iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran. The reaction mixture was then stirred at -78°C and then allowed to warm to 25°C, where it was stirred for 48 h. The reaction mixture was then quenched with a saturated aqueous

acid solution and a saturated aqueous sodium chloride solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-propionamide (295 mg, 67%) as a yellow oil which solidified upon sitting to a yellow solid. The yellow solid was used without further purification: mp 5 112-114°C; EI-HRMS m/e calcd for C₁₄H₁₇ClN₂O₃ (M⁺) 296.0927, found 296.0931.

A solution of 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-propionamide (200 mg, 0.67 mmol) and methyl isocyanate (382 mg, 6.70 mmol) in toluene (3 mL) was heated under reflux (120°C) for 15 h. The reaction mixture was allowed to cool to 25°C and then 10 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1 hexanes/ethyl acetate) afforded 1-[2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea (139 g, 60%) as a white foam: mp 61-64°C (foam to gel); FAB-HRMS m/e calcd for C₁₆H₂₀ClN₃O₄ (M+H)⁺ 354.1220, found 354.1232.

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Example 161**1-[2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea**

A solution of 4-(methylthio)phenylacetic acid (21.21 g, 116.38 mmol) in methanol (291 mL) was treated slowly with concentrated sulfuric acid (3 mL). The resulting reaction 20 mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was diluted with diethyl ether (600 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was dried over sodium sulfate, filtered,

remaining aqueous phase was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded

5 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.52 g, 57%) as a light yellow oil: EI-HRMS m/e calcd for C₁₆H₂₁BrO₂S (M⁺) 356.0446, found 356.0435.

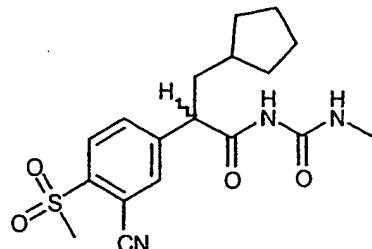
A solution of 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.07 g, 2.99 mmol) in methylene chloride (15 mL) was treated with 3-chloroperoxybenzoic acid (57-86% grade, 1.81 g based on 57%, 5.99 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.09 g, 94%) as a colorless oil: EI-HRMS m/e calcd for C₁₆H₁₉BrO₄S (M⁺) 388.0344, found 388.0343.

20

A solution of 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.62 g, 4.16 mol) in methanol (10 mL) was treated with a 1N aqueous sodium hydroxide solution (8.7 mL, 8.74 mol). The reaction mixture was stirred at 25°C for 27 h. The reaction mixture was concentrated *in vacuo* to remove methanol. The 25 resulting aqueous residue was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 400 mL). The organic layer was washed with water (1 x 300 mL) and washed with a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-

Example 162

1-[2-(3-Cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



A solution of 4-(methylthio)phenylacetic acid (21.21 g, 116.38 mmol) in methanol (291 mL) was treated slowly with concentrated sulfuric acid (3 mL). The resulting reaction mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was diluted with diethyl ether (600 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (4-methylsulfanyl-phenyl)-acetic acid methyl ester (20.95 g, 92%) as a yellow liquid which was used without further purification: EI-HRMS m/e calcd for C₁₀H₁₂O₂S (M⁺) 196.0558, found 196.0559.

15 A solution of (4-methylsulfanyl-phenyl)-acetic acid methyl ester (5.11 g, 26.03 mmol) in carbon tetrachloride (130 mL) was treated slowly with bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred at 25°C for 4 h, at which time, thin layer chromatography still indicated the presence of a substantial amount of starting material. The reaction mixture was further treated with more bromine (1.74 mL, 33.84 mmol). The 20 reaction mixture was stirred an additional 4 h at 25°C and then quenched with a 10% aqueous sodium bisulfite solution (150 mL). The reaction mixture was concentrated *in vacuo* to remove carbon tetrachloride. The resulting aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230

dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.09 g, 94%) as a colorless oil: EI-HRMS m/e calcd for C₁₆H₁₉BrO₄S (M⁺) 388.0344, found 388.0343.

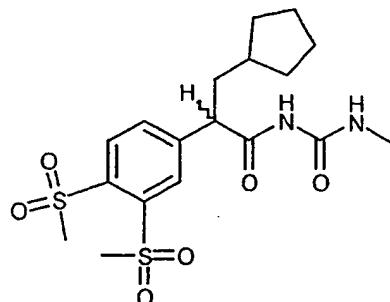
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A mixture of 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (990.0 mg, 2.54 mmol) and copper(I) cyanide (273.3 mg, 3.05 mmol) in dry N,N-dimethylformamide (2.5 mL) was heated under reflux for 4 h. The reaction was allowed to cool to 25°C, and the crude reaction mixture was directly purified without further 10 chemical work-up. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 3/1 hexanes/ethyl acetate) afforded 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (646.5 mg, 76%) as a pale yellow oil: EI-HRMS m/e calcd for C₁₇H₂₁NO₄S (M⁺) 335.1191, found 335.1185.

15 A solution of 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.84 g, 14.4 mol) in tetrahydrofuran (25 mL) was treated with a 0.8M aqueous lithium hydroxide solution (27 mL, 21.6 mmol). The reaction mixture was stirred at 25°C for 2.5 h. The reaction mixture was partitioned between water and ethyl acetate and then acidified to pH = 2 with a 10% aqueous hydrochloric acid solution. The layers were 20 shaken and separated. The resulting organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford crude 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (3.80 g, 82%) as a pale yellow oil that solidified to a pale yellow solid. An analytical sample was obtained by recrystallization from ethyl acetate to afford 2-(3-cyano-4- 25 methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid as a white solid: mp 180-181°C; EI-HRMS m/e calcd for C₁₆H₁₉NO₄S (M⁺) 321.1034, found 321.1039.

Example 163

1-[2-(3,4-Bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



A solution of 3,4-difluorophenylacetic acid (5.00 g, 29.05 mmol) in methanol (73 mL)
5 was slowly treated with concentrated sulfuric acid (4 mL). The resulting reaction mixture
was heated under reflux for 65 h. The reaction mixture was allowed to cool to 25°C and
then concentrated *in vacuo* to remove methanol. The resulting residue was slowly diluted
with a saturated aqueous sodium bicarbonate solution (300 mL) and then extracted with
ethyl acetate (1 x 300 mL). The organic layer was dried over magnesium sulfate, filtered,
10 and concentrated *in vacuo* to afford (3,4-difluoro-phenyl)-acetic acid methyl ester (5.38 g,
99%) as a yellow oil which was used without further purification.

A solution of sodium thiomethoxide (6.39 g, 86.69 mmol) in dimethyl sulfoxide (72 mL)
was treated with (3,4-difluoro-phenyl)-acetic acid methyl ester (5.38 g, 28.89 mmol). The
15 reaction mixture was stirred at 25°C for 2 h and then at 70°C for 15 min. At this time,
thin layer chromatography indicated the absence of starting material and the presence of a
very polar new product. The reaction indicated that the ester hydrolyzed to the acid upon
heating. The resulting reaction mixture was allowed to cool to 25°C. The reaction
mixture was then treated with a 10% aqueous hydrochloric acid solution (200 mL) and
20 then extracted with chloroform (3 x 200 mL). The combined organic layers were dried
over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil. This
yellow oil was dissolved in methanol (100 mL) and then slowly treated with concentrated
sulfuric acid (5 mL). The resulting reaction mixture was heated under reflux for 3 h. The

hexanes/ethyl acetate) afforded an inseparable, isomeric mixture of (3-methanesulfonyl-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-methanesulfonyl-3-methylsulfanyl-phenyl)-acetic acid methyl ester as a yellow liquid (2.19 g, 86%) which was used without further purification and characterization.

5

A solution of the inseparable, isomeric mixture of (3-methanesulfonyl-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-methanesulfonyl-3-methylsulfanyl-phenyl)-acetic acid methyl ester (2.19 g, 7.98 mmol) in methylene chloride (20 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 6.41 g based on 57%, 31.93 mmol).

10 The reaction mixture was stirred at 25°C for 5 h and then slowly quenched with a 1.5N aqueous sodium sulfite solution. The resulting reaction mixture was extracted with methylene chloride (300 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 10/1 methylene chloride/ethyl acetate) afforded (3,4-bis-methanesulfonyl-phenyl)-acetic acid methyl ester (1.89 g, 77%) as a white solid: mp 157-158°C; EI-HRMS m/e calcd for C₁₁H₁₄O₆S₂ (M⁺) 306.0232, found 306.0234.

15

20 A solution of diisopropylamine (951 µL, 6.79 mmol) in dry tetrahydrofuran (6 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (2.5 mL, 6.79 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of (3,4-bis-methanesulfonyl-phenyl)-acetic acid methyl ester (1.89 g, 6.17 mmol) in dry tetrahydrofuran (12 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (4 mL). The resulting reaction mixture was allowed to stir at -78°C for 1 h. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.56 g, 7.40 mmol) in a small amount of dry tetrahydrofuran. The reaction mixture was allowed to warm to 25°C where it was stirred for 64 h. The reaction mixture was quenched with water (150 mL) and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue was further diluted with water (100 mL) and then extracted with

25

A solution of freshly prepared lithium diisopropylamide (35.3 mL of a 0.31M stock solution, 10.9 mmol) cooled to -78°C was treated with (4-fluoro-3-trifluoromethyl-phenyl)-acetic acid (1.11 g, 5.0 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (12.4 mL, 3:1). The resulting solution was stirred at -78°C for 1 h.

5 At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.16 g, 5.52 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.2 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 48 h. This solution was then quenched by the slow addition of the reaction mixture to an aqueous solution of 2N hydrochloric acid (50 mL). The product

10 was extracted into ethyl acetate (3 x 100 mL) and diethyl ether (1 x 50 mL). The organic layers were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (1.28 g, 84.3%) as a white solid: mp 66-68°C; EI-

15 HRMS m/e calcd for C₁₅H₁₆F₄O₂ (M⁺) 305.1165, found 305.1174.

A solution 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (304 mg, 1.0 mmol) in methylene chloride (10 mL) and *N,N*-dimethylformamide (1 drop) was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (1.5 mL, 3.0 mmol). The reaction was stirred for 30 min at 0°C. At this time, 1,1,1,3,3-hexamethyldisilazane (2.0 mL, 9.5 mmol) was added to the reaction mixture. The reaction was allowed to slowly warm to 25°C and then stirred at 25°C for 16 h. The reaction mixture was then treated with methanol (3 mL) and diluted with methylene chloride (35 mL). The resulting mixture was washed with a 5% aqueous sulfuric acid solution (2 x 10 mL), water (1 x 25 mL), and a saturated aqueous sodium chloride solution (3 x 25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionamide (333 mg, 92.5%) as a pale yellow oil: EI-HRMS m/e calcd for C₁₅H₁₇F₄NO (M⁺) 303.1246, found 303.1252.

-321-

acid ethyl ester (28.30 g, 77.2%) as an yellow oil: EI-HRMS m/e calcd for C₁₆H₂₁NO₄ (M⁺) 291.1470, found 291.1470.

A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (7.37 g, 25.3 mmol) in ethyl acetate (316 mL) was treated with 10% palladium on activated carbon (500 mg). The reaction mixture was stirred under hydrogen gas at 60 psi at 25°C for 18 h. The catalyst was then filtered off through a pad of celite (ethyl acetate). The filtrate was concentrated *in vacuo* to give 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (3.52 g, 53.3%) as a yellow oil: EI-HRMS m/e calcd for C₁₆H₂₃NO₂ (M⁺) 261.1727, found 261.1727.

A mixture of concentrated hydrochloric acid (0.38 mL) and ice (380 mg) cooled to 0°C was treated with 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (497 mg, 1.90 mmol). After 5 min, a solution of sodium nitrite (139 mg, 2.0 mmol) in water (0.31 mL) was added to the reaction mixture. The resulting solution was stirred at 0°C for 5 min. At this time, this solution was added to a solution of *n*-butyl mercaptan (0.23 mL, 2.20 mmol) in water (0.4 mL) warmed to 45°C. The reaction was stirred at 45°C for 3 h. At this time, the reaction was diluted with water (50 mL) and extracted with methylene chloride (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude brown oil (588 mg) in methylene chloride (16.5 mL) was cooled to 0°C and treated with 3-chloroperoxybenzoic acid (80-85% grade, 1.5 g, 8.78 mmol). The reaction mixture was stirred at 25°C for 48 h. At this time, the reaction was diluted with methylene chloride (100 mL). This solution was washed with a saturated aqueous sodium bisulfite solution (1 x 100 mL), a saturated aqueous sodium chloride solution (1 x 100 mL), a saturated aqueous sodium bicarbonate solution (1 x 100 mL), and a saturated aqueous sodium chloride solution (1 x 100 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 2-[4-(butane-

was stirred at 25°C for 48 h. This solution was then quenched by the slow addition of the reaction mixture to an aqueous solution of 2N hydrochloric acid (50 mL). The product was extracted into ethyl acetate (3 x 100 mL) and diethyl ether (1 x 50 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (1.28 g, 84.3%) as a white solid: mp 66-68°C; EI-HRMS m/e calcd for C₁₅H₁₆F₄O₂ (M⁺) 305.1165, found 305.1174.

10 A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (7.77 g, 25.3 mmol) in methanol (50 mL) was treated slowly with concentrated sulfuric acid (0.01 mL). The resulting reaction mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (75 mL) and washed with a saturated aqueous sodium bicarbonate solution (1 x 50 mL), water (1 x 50 mL), and a saturated aqueous sodium chloride solution (4 x 50 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid methyl ester (8.48 g, 87.5%) as yellow oil: EI-HRMS m/e calcd for C₁₆H₁₈F₄O₂ (M⁺) 318.1243, found 318.1240.

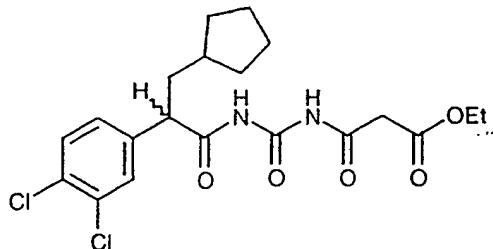
20

A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid methyl ester (7.0 g, 21.9 mmol) in N,N-dimethylformamide (50 mL) was treated with sodium methanethiolate (2.61 g, 33.0 mmol). The reaction mixture was then heated to 100-110°C for 24 h. At this time, the reaction was poured onto a mixture of ice and an aqueous solution of 2N hydrochloric acid (100 mL). This mixture was extracted into ethyl acetate (3 x 75 mL) and diethyl ether (1 x 50 mL). The organics were then washed with water (1 x 75 mL) and a saturated aqueous sodium chloride solution (3 x 100 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 85/15

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Example 167

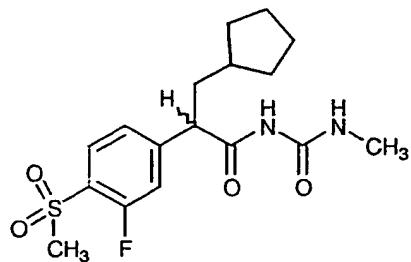
3-{3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic acid ethyl ester



5 A solution of [3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea (prepared in Example 1B-d, 402 mg, 1.22 mmol) and pyridine (0.15 mL, 1.83 mmol) in toluene (15 mL) was treated with ethyl malonyl chloride (0.19 mL, 1.5 mmol). The resulting reaction mixture was heated at reflux for 2 h. At this time, additional pyridine (0.15 mL, 1.83 mmol) and ethyl malonyl chloride (0.19 mL, 1.5 mmol) were added. The reaction was
10 then heated at reflux for 90 min. The reaction was then cooled to 25°C, diluted with ethyl acetate (50 mL), washed with water (2 x 25 mL), and dried over magnesium sulfate. The solution was concentrated *in vacuo*. Flash column chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexane/ethyl acetate) afforded 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic acid ethyl ester (172 mg, 32%) as a colorless
15 gum: EI-HRMS m/e calcd for C₂₀H₂₄Cl₂N₂O₅ (M⁺) 443.1140, found 443.1128.

Example 168

1-[3-Cyclopentyl-2-(3-fluoro-4-methanesulfonyl-phenyl)-propionyl]-3-methyl-urea



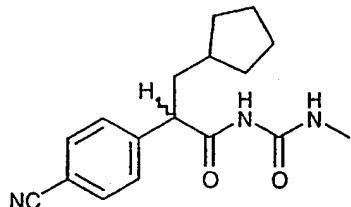
A solution of 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (1.00 g, 3.21 mmol) and sodium methanesulfinate (0.36 g, 3.53 mmol) in dimethyl sulfoxide (3 mL) was heated at 130°C for 5 h. The black reaction mixture was then poured over ice (20 g), resulting in the formation of a brown sticky substance. The resulting mixture was 5 then treated with ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4- 10 methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (0.95 g, 84%) as a yellow gel: FAB-HRMS m/e calcd for C₁₆H₂₁NO₆S (M+H)⁺ 356.1169, found 356.1175.

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (1.50 g, 4.22 mmol) in methanol (30 mL) was treated with a solution of ammonium 15 chloride (474 mg, 8.86 mmol) in water (3 mL). The reaction mixture was stirred at 25°C for 5 min and then treated with zinc dust (2.70 g, 41.36 mmol). The reaction mixture was heated under reflux for 2 h. The reaction mixture was allowed to cool to 25°C and then filtered through a pad of celite. The filtrate was concentrated *in vacuo*. The resulting orange oil was dissolved in ethyl acetate, dried over magnesium sulfate, filtrated, and 20 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1 hexanes/ethyl acetate) afforded 2-(3-amino-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.49 g, 98%) as a white solid: mp 98-100°C; EI-HRMS m/e calcd for C₁₆H₂₃NO₄S (M⁺) 325.1348, found 325.1358.

25 A slurry of nitrosonium tetrafluoroborate (215 mg, 1.84 mmol) in methylene chloride (6 mL) cooled to 0°C was treated dropwise with a solution of 2-(3-amino-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (500 mg, 1.54 mmol) in a small amount of methylene chloride. The resulting reaction mixture was stirred at 0°C for 1 h. The reaction mixture was then allowed to warm to 25°C and then treated

Example 169

1-[2-(4-Cyano-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea

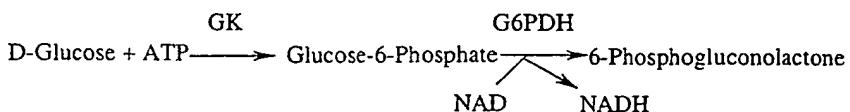


A solution of (4-bromo-phenyl)-acetic acid (6.77 g, 31.48 mmol) in methanol (32 mL)
5 was treated with a catalytic amount of concentrated sulfuric acid (3 drops). The reaction mixture was then heated to reflux for 24 h. At this time, the reaction was concentrated *in vacuo*. The residue was treated with an aqueous solution of sodium bicarbonate (100 mL). This solution was extracted with ethyl acetate (3 x 100 mL). The organic layers were washed with a saturated aqueous solution of sodium chloride, dried over sodium
10 sulfate, filtered and concentrated *in vacuo* to afford (4-bromo-phenyl)-acetic acid methyl ester (6.75 g, 94%) as a yellow oil. The product was used without further purification.

A solution of freshly prepared lithium diisopropylamide (50.5 mL of 0.3 M, 15.15 mmol) cooled to -78°C was treated with (4-bromo-phenyl)-acetic acid methyl ester (3.36 g, 14.67 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (37 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (3.24 g, 15.45 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.24 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was warmed to 25°C and stirred at 25°C for 20 h. The reaction mixture was then quenched by the slow addition of a saturated ammonium chloride solution (40 mL). The reaction mixture was then poured into water (100 mL) and the product was extracted into ethyl acetate (3 x 75 mL). The organics were washed with a saturated aqueous sodium chloride solution (3 x 100 mL) and a saturated aqueous solution of lithium chloride (3 x 100 mL), dried over sodium sulfate and magnesium
20 sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60,
25

Biological Activity Examples**Example A: *In Vitro* Glucokinase Activity**

Glucokinase Assay: Glucokinase (GK) was assayed by coupling the production of glucose-6-phosphate to the generation of NADH with glucose-6-phosphate dehydrogenase (G6PDH, 0.75-1 kunits/mg; Boehringer Mannheim, Indianapolis, IN) from *Leuconostoc mesenteroides* as the coupling enzyme (Scheme 2).



Scheme 2

10

Recombinant Human liver GK1 was expressed in *E. coli* as a glutathione S-transferase fusion protein (GST-GK) [Liang et al, 1995] and was purified by chromatography over a glutathione-Sepharose 4B affinity column using the procedure provided by the manufacturer (Amersham Pharmacia Biotech, Piscataway, NJ). Previous studies have demonstrated that the enzymatic properties of native GK and GST-GK are essentially identical (Liang et al, 1995; Neet et al., 1990).

The assay was conducted at 25° C in a flat bottom 96-well tissue culture plate from Costar (Cambridge, MA) with a final incubation volume of 120 µL. The incubation mixture contained: 25 mM Hepes buffer (pH, 7.1), 25 mM KCl, 5 mM D-glucose, 1 mM ATP, 1.8 mM NAD, 2 mM MgCl₂, 1 µM sorbitol-6-phosphate, 1 mM dithiothreitol, test drug or 10% DMSO, 1.8 unit/ml G6PDH, and GK (see below). All organic reagents were > 98 % pure and were from Boehringer Mannheim with the exceptions of D-glucose and Hepes that were from Sigma Chemical Co, St Louis, MO. Test compounds were dissolved in DMSO and were added to the incubation mixture minus GST-GK in a volume of 12 µL to yield a final DMSO concentration of 10%. This mix was preincubated

Example B: *In Vivo* Glucokinase Activity**Glucokinase Activator *in vivo* Screen Protocol**

5 C57BL/6J mice are orally dosed via gavage with Glucokinase (GK) activator at 50 mg/kg body weight following a two hour fasting period. Blood glucose determinations are made five times during the six hour post-dose study period.

Mice (n=6) are weighed and fasted for a two hour period prior to oral treatment.
10 GK activators are formulated at 6.76 mg/ml in Gelucire vehicle (Ethanol:Gelucire44/14:PEG400q.s. 4:66:30 v/w/v. Mice are dosed orally with 7.5 μ L formulation per gram of body weight to equal a 50 mg/kg dose. Immediately prior to dosing, a pre dose (time zero) blood glucose reading is acquired by snipping off a small portion of the animals tail (~1 mm) and collecting 15 μ L blood into a heparinized
15 capillary tube for analysis. Following GK activator administration, additional blood glucose readings are taken at 1, 2, 4, and 6 hours post dose from the same tail wound. Results are interpreted by comparing the mean blood glucose values of six vehicle treated mice with six GK activator treated mice over the six hour study duration. Compounds are considered active when they exhibit a statistically significant ($p \leq 0.05$) decrease in blood
20 glucose compared to vehicle for two consecutive assay time points.

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R⁴⁰ is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl, -(CH₂)_n-C(O)OR⁵ or -C(O)-(CH₂)_n-C(O)OR⁶;

R⁵ is hydrogen, lower alkyl or perfluoro-lower alkyl;

R⁶, R⁷ and R⁸ are independently hydrogen or lower alkyl; and

5 n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

10 R¹ and R² are independently hydrogen, halo, amino, hydroxyamino, cyano, nitro, lower alkyl, -OR⁵, -C(O)OR⁵, perfluoro-lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or sulfonamido;

R³ is cycloalkyl having from 3 to 7 carbon atoms;

15 R⁴ is an unsubstituted or mono-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amine group shown, which five- or six-membered heteroaromatic ring contains from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono-substituted heteroaromatic ring being monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano, -(CH₂)_n-OR⁶, -(CH₂)_n-C(O)OR⁷, -(CH₂)_n-C(O)NHR⁶, -C(O)-C(O)OR⁸ or -(CH₂)_n-NHR⁶;

20 n is 0, 1, 2, 3 or 4;

R⁵ is hydrogen, lower alkyl, or perfluoro-lower alkyl; and

25 R⁶, R⁷ and R⁸ are independently hydrogen or lower alkyl;

or a pharmaceutically acceptable salt thereof.

9. A compound according to any of claims 1 to 8, wherein R² is hydrogen, lower alkyl sulfonyl, perfluoro-lower alkyl, perfluoro-lower alkyl sulfonyl, halo or -OR⁵ wherein R⁵ is perfluoro-lower alkyl.
5
10. A compound according to any of claims 1 to 9, wherein R² is halo or lower alkyl sulfonyl.
11. A compound according to any of claims 1 to 10, wherein the amide is in the R
10 configuration at the asymmetric carbon shown.
12. A compound according to any of claims 1 to 11, wherein R³ is cyclopentyl, cyclohexyl or cycloheptyl.
- 15 13. A compound according to any of claims 1 to 12, wherein R³ is cyclopentyl.
14. A compound according to any of claims 1 to 13, selected from the group consisting of:
20 2-(3-chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
2-(4-bromo-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
2-(4-chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethyl-phenyl)-propionamide,
3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide,
25 3-cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide,
3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(4-nitrophenyl)-N-thiazol-2-yl-propionamide,
2-(4-amino-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
2-(3-amino-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
30 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
2-(4-cyano-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,

3-cyclopentyl-2-(3-fluoro-4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-hydroxymethyl-thiazol-2-yl)-
propionamide,
5 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-
propionamide,
2-(4-chloro-phenyl)-3-cyclopentyl-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide,
10 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-hydroxymethyl-thiazol-2-yl)-
propionamide,
3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-methanesulfonyl-phenyl)-
15 propionamide,
3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-2-(4-methanesulfonyl-phenyl)-
propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-methyl-thiazol-2-yl)-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-thiazol-2-yl)-propionamide,
15 {2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid
ethyl ester,
{2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid
methyl ester,
20 2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid
methyl ester,
2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid
ethyl ester,
25 {2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid
ethyl ester,
2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid
ethyl ester,
30 {2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid
methyl ester,
{2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid,
35 {2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid
ethyl ester,
2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-5-carboxylic
acid,

3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-nitro-thiazol-2-yl)-propionamide,
3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide,
3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide,
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethyl-phenyl)-2-propionamide,
5 3-cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide,
2-(3-chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
2-(4-amino-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
2-(4-cyano-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
2-(4-chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
10 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
3-cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide,
2-(4-cyano-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
3-cyclopentyl-2-(4-methylsulfanyl-phenyl)-N-pyridin-2-yl-propionamide,
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethylsulfanyl-phenyl)-propionamide,
15 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide,
3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide,
2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-
propionamide,
20 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-
propionamide,
3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide,
2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-
propionamide,
25 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-pyridin-2-yl-
propionamide,
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,
3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-carboxymethylpyridin)-2-yl-
propionamide,
30 6-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl
ester,
6-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid,
6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,
6-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,

3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-nitropyridin)-2-yl-propionamide,
3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-methylpyridin)-2-yl-propionamide,
3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(4-methylpyridin)-2-yl-propionamide,
3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(6-methylpyridin)-2-yl-propionamide,
5 3-cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,
3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-(5-methyl-pyridin-2-yl)-propionamide,
10 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-N-methyl-nicotinamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(1H-imidazol-2-yl)-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-isoxazol-3-yl)-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-oxazol-2-yl-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyridazin-3-yl-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyrimidin-2-yl-propionamide,
15 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyrimidin-6-yl-propionamide,
3-cyclopentyl-2-(4-nitro-phenyl)-N-pyrimidin-4-yl-propionamide,
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-[1,3,4]thiadiazol-2-yl-propionamide,
2-[4-methanesulfonyl phenyl]-3-cyclohexyl N-thiazol-2-yl-propionamide, and
2-[4-methanesulfonyl phenyl]-3-cycloheptyl N-thiazol-2-yl-propionamide.
20 15. A compound according to any of claims 1 to 13, selected from the group consisting of:
1-(3-cyclopentyl-2-phenyl-propionyl)-3-methyl-urea,
1-[2-(3-chloro-phenyl)-3 cyclopentyl-propionyl]-3-methyl-urea,
1-[2-(4-chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,
25 1-[2-(4-cyano-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,
1-[2-(4-bromo-phenyl)-3-cyclopentyl-propionyl]-3-methyl urea,
[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,
30 1-allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-proprionyl]-urea,
1-allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-proprionyl]-urea,
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,

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3-[cyclohexyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,
[3-cyclohexyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,
[3-cycloheptyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,
5 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid
ethyl ester,
{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl
ester,
{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid methyl
ester,
10 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid
methyl ester,
{3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl
ester,
15 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic
acid ethyl ester,
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea,
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea,
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea,
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea,
20 1-(2-chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea, and
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea.

16. A compound according to any of claims 1 to 14, selected from the group consisting of:
3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide,
25 3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethoxy-phenyl)-propionamide,
3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,
3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide,
6-[3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid
methyl ester,
30 N-(5-Chloro-pyridin-2-yl)-3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide,
3-Cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,
3-Cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-
propionamide,
35 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl)
propionamide,

17. A compound according to any of claims 1 to 13 and 15, selected from the group consisting of:

5 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl urea,
1-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionyl]-3-methyl urea,
1-Allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea,
1-[2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,
10 1-[2(R)-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea, and
1-[2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea.

18. The use of the compounds according to any of claims 1 to 17 for the treatment of type
15 II diabetes.

19. A pharmaceutical composition comprising a compound of any of claims 1 to 17 and a
pharmaceutically acceptable carrier and/or adjuvant.

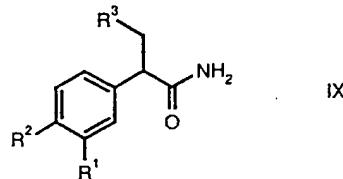
20 20. The use of a compound according to any of claims 1 to 17 for the preparation of
medicaments containing a compound according to any of claims 1 to 17 for the
treatment or prophylaxis of type II diabetes.

21. A method for the prophylactic or therapeutic treatment of type II diabetes, which
25 method comprises administering a compound of any of claims 1 to 17 to a human being
or an animal.

22. A process for the preparation of the compounds of formula I according to any of
claims 1 to 17, which process comprises:

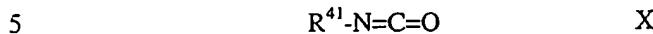
-349-

(b) The reaction of a compound of formula IX:



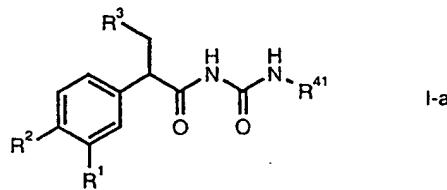
wherein R^1 , R^3 and R^5 are as defined in claim 1;

with a compound of the formula X:



wherein R⁴¹ is lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl or -(CH₂)_n-C(O)OR⁵, wherein R⁵ is hydrogen or lower alkyl and n is as defined above;

to produce a compound of formula I-a:

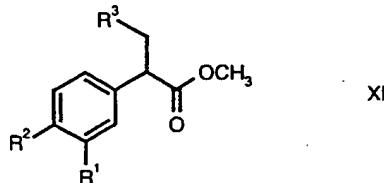


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wherein R^1 , R^2 , R^3 and R^{41} are as defined above;

optionally followed by the conversion of one or both of the substituents R¹ and/or R² into another substituent R¹ and/or R² as defined in claim 1.

15 (c) The reaction of a compound of the formula XI:



wherein R¹, R² and R³ are as defined in claim 1;

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optionally followed by the conversion of one or both of the substituents R¹ and/or R² into another substituent R¹ and/or R² as defined in claim 1.

23. The invention as described hereinbefore.

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INTERNATIONAL SEARCH REPORT

Inte...onal Application No
PCT/EP 00/02450

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D277/46	A61K31/426	C07D277/56	C07D213/75	C07D213/80
	C07D213/82	C07D213/85	C07D233/88	C07D237/20	C07D239/42
	C07D241/20	C07D253/06	C07D261/14	C07D263/48	C07D285/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 249 241 C (BAYER) 13 July 1912 (1912-07-13) see example 1 page 1, right-hand column, line 46 - line 50; claim 1	1,5
X	SPIELMAN M. A. ET AL.: "Anticonvulsant Drugs. II. Some Acylureas" JOURNAL OF AMERICAN CHEMICAL SOCIETY, vol. 70, 1948, pages 4189-4191, XP000940775 page 4190; table 1	1,5
A	US 3 776 917 A (MANN T ET AL) 4 December 1973 (1973-12-04) column 1, line 23 - line 60 column 6, line 31 - line 57	1-22

Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search Date of mailing of the international search report

13 October 2000

26.10.00

Name and mailing address of the ISA

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Authorized officer

Schmid, J-C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/02450

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 23 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The scope of claim 23 is unclear
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/02450

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 249241	C	NONE	
US 3776917	A 04-12-1973	NONE	

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1883